

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



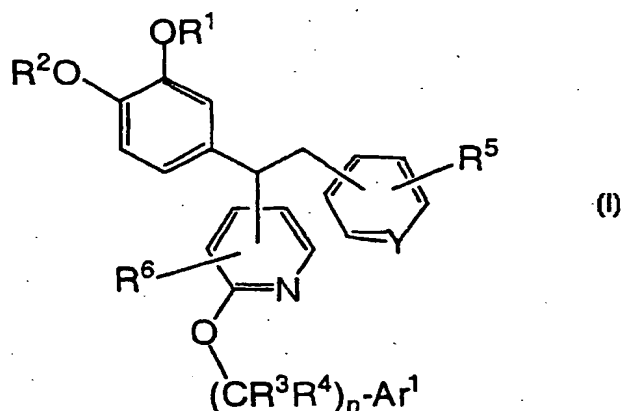
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 213/89, 213/64, 409/14, 417/14, 213/79, 213/76, 405/14, A61K 31/4427, A61P 11/00		A2	(11) International Publication Number: WO 00/64874 (43) International Publication Date: 2 November 2000 (02.11.00)
(21) International Application Number: PCT/CA00/00427 (22) International Filing Date: 19 April 2000 (19.04.00) (30) Priority Data: 60/130,690 23 April 1999 (23.04.99) US		16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). (74) Agents: MURPHY, Kevin, P. et al.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montreal, Québec H3A 2Y3 (CA). (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, VZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): MERCK FROSST CANADA & CO. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): FRENETTE, Richard [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). FRIESEN, Richard [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). GIRARD, Mario [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). GIRARD, Yves [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). GODBOUT, Cedrickx [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). GUAY, Daniel [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). HAMEL, Pierre [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Québec H9H 3L1 (CA). PERRIER, Helene [CA/CA];		Published Without international search report and to be republished upon receipt of that report.	

(54) Title: HETEROSUBSTITUTED PYRIDINE DERIVATIVES AS PDE 4 INHIBITORS

(57) Abstract

The invention encompasses the novel compound of Formula (I) useful in the treatment of diseases, including asthma, by raising the level of cyclic adenosine-3',5'-monophosphate (cAMP) through the inhibition of phosphodiesterase IV (PDE 4). The invention also encompasses pharmaceutical compositions and methods for treatment.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

TITLE OF THE INVENTION

HETEROSUBSTITUTED PYRIDINE DERIVATIVES AS *PDE 4* INHIBITORS

BACKGROUND OF THE INVENTION

5 This invention relates to compounds and pharmaceutical compositions containing such compounds useful for treating diseases by raising the level of cyclic adenosine-3',5'-monophosphate (cAMP) through the inhibition of phosphodiesterase IV (PDE 4).

 Many hormones and neurotransmitters modulate tissue function by
10 elevating intra-cellular levels of 3',5'-cyclic adenosine monophosphate (cAMP). The cellular levels of cAMP are regulated by mechanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenylyl cyclase which may be directly activated by agents such as forskolin or indirectly activated by the binding of specific agonists to cell surface receptors which are coupled to adenylyl cyclase. The
15 breakdown of cAMP is controlled by a family of phosphodiesterase (PDE) isoenzymes, which also control the breakdown of guanosine 3',5'-cyclic monophosphate (cGMP). To date, nine members of the family have been described (PDE 1-9) the distribution of which varies from tissue to tissue. This suggests that specific inhibitors of PDE isoenzymes could achieve differential elevation of cAMP
20 in different tissues, [for reviews of PDE distribution, structure, function and regulation, see Beavo & Reifsnnyder (1990) TIPS, 11: 150-155, Nicholson et al (1991) TIPS, 12: 19-27 and Houslay et al (1998) Adv. Pharmacol. 44: 225-342].

 The availability of PDE isotype selective inhibitors has enabled the role of PDEs in a variety of cell types to be investigated. In particular it has been
25 established that PDE 4 controls the breakdown of cAMP in many inflammatory cells, for example, basophils (Peachell P.T. et al., (1992) J. Immunol. 148 2503-2510) and eosinophils (Dent G. et al., (1991) Br. J. Pharmacol. 103 1339-1346) and that inhibition of this isotype is associated with the inhibition of cell activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect.
30 Consequently PDE 4 inhibitors are currently being developed as potential anti-inflammatory drugs particularly for the prophylaxis and treatment of asthma, by achieving both anti-inflammatory and bronchodilator effects.

 The application of molecular cloning to the study of PDEs has revealed that for each isotype there may be one or more isoforms. For PDE 4, it has been
35 shown that there are four isoforms (A, B, C and D) each coded for by a separate gene

in both rodents (Swinnen J.V. et al., (1989) Proc. Natl. Acad. Sci. USA 86 5325-5329) and man (Bolger G. et al., (1993) Mol. Cell Biol. 13 6558-6571).

The existence of multiple PDE 4s raises the prospect of obtaining inhibitors that are selective for individual isoforms, thus increasing the specificity of action of such inhibitors. This assumes that the different PDE 4 isoforms are functionally distinct. Indirect evidence in support of this comes from the selective distribution of these isoforms in different tissues (Swinnen et al., 1989; Bolger et al., 1993; Obermolte R. et al., (1993) Gene 129 239-247, *ibid*) and the high degree of sequence conservation amongst isoforms of different species.

To date full length cDNAs for human PDE 4A, B, C and D (Bolger et al., 1993 *ibid*; Obermolte et al., 1993 *ibid*; McLaughlin M. et al., (1993) J. Biol. Chem. 268 6470-6476, Owens et al (1997) Cell. Signal., 9: 575-585) and rat PDE 4A, B and D (Davis R. et al., (1989) Proc. Natl. Acad. Sci. USA 86 3604-3608; Swinnen J.V. et al., (1991) J. Biol. Chem. 266 18370-18377), have been reported, enabling functional recombinant enzymes to be produced by expression of the cDNAs in an appropriate host cell. These cDNAs have been isolated by conventional hybridisation methods.

The design of PDE 4 inhibitors for the treatment of inflammatory diseases such as asthma, has met with limited success to date. Many of the PDE 4 inhibitors which have been synthesised have lacked potency and/or inhibit more than one type of PDE isoenzyme in a non-selective manner. PDE 4 inhibitors that are relatively potent and selective for PDE 4, are reported to be emetic as well. Indeed this side effect has been so universal that experts have expressed their belief that the emesis experienced upon administration of a PDE 4 inhibitor, may be mechanism based.

One object of the present invention is to provide heterosubstituted pyridines derivatives that are inhibitors of PDE 4 at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit the human recombinant PDE 4 enzyme and also elevate cAMP in isolated leukocytes. The compounds thus prevent, alleviate or reduce inflammation in the lungs, such as that induced by carrageenan, platelet-activating factor (PAF), interleukin-5 (IL-5) or antigen challenge. The compounds also suppress the hyperresponsiveness of airway smooth muscle seen in inflamed lungs.

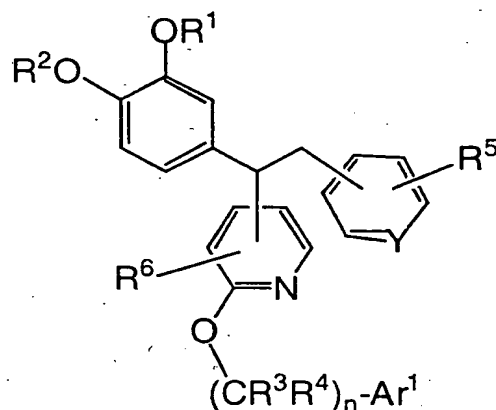
Another object of the present invention is to provide compounds that have good oral activity and that at orally effective doses, exhibit a reduced incidence of the side-effects associated with known PDE 4 inhibitors, such as rolapram. The

compounds of the invention are therefore of use in medicine, especially in the prophylaxis and treatment of asthma and other inflammatory conditions.

SUMMARY OF THE INVENTION

5

A compound represented by formula I:



or a pharmaceutically acceptable salt or hydrate thereof wherein:

Y represents N or N-oxide;

10 R¹ and R² are independently selected from:

H, C₁₋₆alkyl and haloC₁₋₆ alkyl,

R³ and R⁴ are independently selected from H and C₁₋₆alkyl, or R³ and R⁴ attached to the same carbon atom taken together represent a carbonyl oxygen atom; or

15 R³ and R⁴ attached to different carbon atoms considered in combination with the carbon atoms to which they are attached along with any intervening atoms and represent a saturated 5, 6 or 7 membered carbocyclic ring,

n represents an integer of from 0-6;

20

Ar¹ is selected from the group consisting of:

(a) thienyl,

(b) thiazolyl,

(c) pyridyl,

25 (d) phenyl and

(e) naphthyl,

said Ar¹ being optionally substituted with 1-3 members selected from the group consisting of:

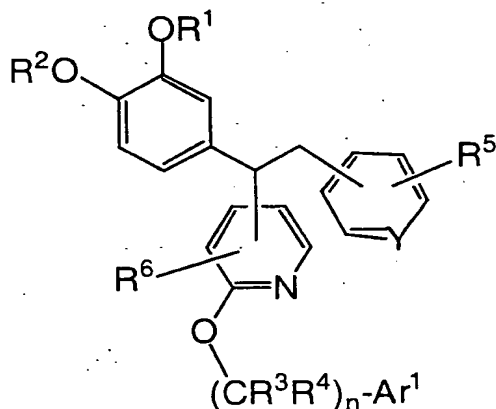
- 5 (1) halo,
- (2) C₁-6alkoxy,
- (3) C₁-7alkylthio,
- (4) CN,
- (5) C₁-6alkyl,
- 10 (6) C₁-6hydroxyalkyl,
- (7) -CO₂H, -CO₂C₁-6alkyl,
- (8) NH(SO₂Me), N(SO₂Me)₂,
- (9) SO₂Me,
- (10) NO₂,
- 15 (11) C₁-6alkenyl,
- (12) halo C₁-6 alkyl, and
- (13) NH₂,

and when Ar¹ represents a phenyl or naphthyl group with two or three substituents, two such substituents may be considered in combination and represent a 5 or 6 membered fused lactone ring.

Pharmaceutical compositions and methods of treatment are also included.

25 DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds represented by formula I:



as well as pharmaceutically acceptable salts or hydrate thereof wherein:

Y represents N or N-oxide;

- 5 R¹ and R² are independently selected from:
H, C₁-6alkyl and haloC₁-6 alkyl,

R³ and R⁴ are independently selected from H and C₁-6alkyl, or R³ and R⁴ attached to the same carbon atom taken together represent a carbonyl oxygen atom, or

- 10 R³ and R⁴ attached to different carbon atoms considered in combination with the carbon atoms to which they are attached along with any intervening atoms and represent a saturated 5, 6 or 7 membered carbocyclic ring,

n represents an integer of from 0-6;

15

Ar¹ is selected from the group consisting of:

- (a) thienyl,
(b) thiazolyl,
(c) pyridyl,
20 (d) phenyl and
(e) naphthyl,

said Ar¹ being optionally substituted with 1-3 members selected from the group consisting of:

- 25 (1) halo,

- (2) C₁-6alkoxy,
- (3) C₁-7alkylthio,
- (4) CN,
- (5) C₁-6alkyl,
- 5 (6) C₁-6hydroxyalkyl,
- (7) -CO₂H, -CO₂C₁-6alkyl,
- (8) NH(SO₂Me), N(SO₂Me)₂,
- (9) SO₂Me,
- (10) NO₂,
- 10 (11) C₁-6alkenyl,
- (12) halo C₁-6 alkyl, and
- (13) NH₂,

and when Ar¹ represents a phenyl or naphthyl group with two or three substituents, two such substituents may be considered in combination and represent a 5 or 6 membered fused lactone ring.

The following definitions pertain to the terms used herein unless otherwise indicated.

Halo is intended to include F, Cl, Br, and I. HaloC₁-6 alkyl refers to an alkyl group having 1-9 halo groups attached. Examples include -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CHFCH₂F, -CF₂CH₂F, -CF₂CHF₂ and -CF₂CF₃.

Alkyl groups include straight or branched alkyl groups having 1-7 carbon atoms, and cyclic alkyl groups having from 3-7 carbon atoms. Cycloalkyl groups with alkyl substituent groups attached are also included. Examples of C₁-6alkyl groups include methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of C₁-6alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

Likewise, C₁-7alkylthio is intended to include alkylthio groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies -SCH₂CH₂CH₃.

Preferred values of R¹ and R² are C₁-6 alkyl and haloC₁-6alkyl. More preferred values are selected from the group consisting of CH₃, CH₂F, CHF₂, CF₃

and most preferably CHF₂. Within this subset, all other variables are as originally defined.

Preferred values of n are 0, 1, 2 and 3. More preferred values are 0, 1 and 2. Within these subsets, all other variables are as originally defined.

5 Preferred values of Ar¹ are phenyl and naphthyl. More preferred is phenyl. Within these subsets, all other variables are as originally defined.

Preferred values of R³ and R⁴ are H and C₁₋₆alkyl. More preferred are H and methyl. Within these subsets, all other variables are as originally defined.

10 Preferred values of R⁵ and R⁶ are H and C₁₋₆alkyl. More preferred is H. Within these subsets, all other variables are as originally defined.

Preferably the Y is in the 2, 3 or 4 position relative to the point of attachment to the ethylene group. More preferably the Y is in the 4 position relative to the point of attachment to the ethylene group.

15 Similarly, the pyridyl nitrogen atom shown is preferably in the 2, 3 or 4 position, relative to the attachment to the ethylene group. More preferably it is in the 3 position.

A subset of compounds that is of particular interest relates to compounds of formula I wherein:

20 R¹ and R² are C₁₋₆alkyl and haloC₁₋₆alkyl selected from the group consisting of CH₃, CH₂F, CHF₂ and CF₃ ;

n is 0, 1, 2 or 3;

Ar¹ is phenyl or naphthyl;

R³ and R⁴ are H and methyl and

R⁵ and R⁶ are H or C₁₋₆alkyl.

25 Within this subset, all other variables are as originally defined.

More particularly, a subset of compounds that is of particular interest relates to compounds of formula I wherein:

R¹ and R² are CHF₂, and n is 0, 1 or 2. Within this subset, all other variables are as defined immediately above.

30 Another subset of compounds that is of particular interest relates to compounds of formula I wherein:

R¹ and R² are CHF₂;

n is 0, 1 or 2;

R³ and R⁴ are H or methyl, R⁵ and R⁶ are H and

Ar¹ is phenyl.

Within this subset, all other variables are as defined immediately above.

Examples of compounds falling within the present invention include the following:

- 5 1. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(trifluoromethoxy)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
2. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-methoxycarbonyl)phenoxy]3-pyridyl]ethyl}pyridine,
3. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-methoxycarbonyl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
- 10 4. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(2-hydroxypropan-2-yl)phenoxy]3-pyridyl]ethyl}pyridine,
5. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(2-hydroxypropan-2-yl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
- 15 6. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-nitrophenoxy)3-pyridyl]ethyl}pyridine-N-oxide,
7. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(methylsulfonylamino)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
8. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(trifluoromethyl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
- 20 9. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[3-(methylsulfonylamino)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
10. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(2-propenyl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
- 25 11. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(2-propyl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
12. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(dimethylsulfonylamino)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
13. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[(4-hydroxymethyl-3-carboxyl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide sodium salt,
- 30 14. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(benzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
15. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(1-phenylethoxy)3-pyridyl]ethyl}pyridine-N-oxide,

16. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,4-difluorobenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
17. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-methylsulfonylbenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
- 5 18. (Enantiomer-1)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,5-difluorobenzyloxy)3-pyridyl]ethyl}pyridine,
19. (Enantiomer-2)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,5-difluorobenzyloxy)3-pyridyl]ethyl}pyridine,
20. (Enantiomer-1)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,5-difluorobenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
- 10 21. (Enantiomer-2)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,5-difluorobenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
22. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-methyl-2-(4-fluorophenyl)propyloxy]3-pyridyl]ethyl}pyridine,
- 15 23. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-methyl-2-(4-fluorophenyl)propyloxy]3-pyridyl]ethyl}pyridine-N-oxide,
24. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-(4-fluorophenyl)ethoxy]3-pyridyl]ethyl}pyridine,
25. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-(4-fluorophenyl)ethoxy]3-pyridyl]ethyl}pyridine-N-oxide,
- 20 26. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-trifluoromethylbenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
27. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-trifluoromethoxybenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
- 25 28. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(1,1-dimethyl-2-phenylethoxy)3-pyridyl]ethyl}pyridine-N-oxide,
29. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(2-thienylmethoxy)3-pyridyl]ethyl}pyridine-N-oxide,
30. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[1-methyl-1-(4-fluorophenyl)ethoxy]3-pyridyl]ethyl}pyridine,
- 30 31. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[1-methyl-1-(4-fluorophenyl)ethoxy]3-pyridyl]ethyl}pyridine-N-oxide,
32. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-fluorobenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,

33. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-chlorobenzoyloxy)3-pyridyl]ethyl}pyridine-N-oxide,

34. 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[1,2-dihydro-1-isobenzofuranone-6-oxy]3-pyridyl]ethyl}pyridine-N-oxide.

5 As used herein, the terms "Enantiomer-1" and "Enantiomer-2" refer respectively to the fast eluting isomer and the slow eluting isomer when purified by HPLC.

The compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present
10 invention is meant to include all such possible isomers and diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

The invention also encompasses a pharmaceutical composition that is comprised of a compound of formula I in combination with a pharmaceutically
15 acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

Moreover, within this preferred embodiment, the invention
20 encompasses a pharmaceutical composition for the treatment or prevention of disease by inhibition of PDE 4, resulting in an elevation of cAMP, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

The term "pharmaceutically acceptable salts" refers to salts prepared
25 from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from
30 pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, *N,N*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine,
35

isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

5 It will be understood that references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The compounds of formula I are selective and potent inhibitors of PDE
4. The biological activity and utility of the compounds may be demonstrated as described herein.

10 The compounds according to the invention are thus of particular use in the prophylaxis and treatment of human diseases where an unwanted inflammatory response or muscular spasm (for example bladder or alimentary smooth muscle spasm) is present and where elevation of the cAMP levels may be expected to prevent or alleviate the disease or condition.

15 Particular uses to which the compounds of the invention may be put include the prophylaxis and treatment of asthma, especially inflamed lung associated with asthma, cystic fibrosis, in the treatment of inflammatory airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory
20 arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and atherosclerosis.

The compounds of the invention also suppress neurogenic inflammation. They are, therefore, analgesic, antitussive and antihyperalgesic in
25 inflammatory diseases associated with irritation and pain.

The compounds also elevate cAMP in lymphocytes and thereby suppress unwanted lymphocyte activation in immune-based diseases such as rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease.

30 The compounds also reduce gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion of gastric acid.

The compounds also suppress cytokine synthesis by inflammatory cells in response to immune or infectious stimulation. They are, therefore, useful in the treatment of bacterial, fungal or viral induced sepsis and septic shock in which
35 cytokines such as tumour necrosis factor (TNF) are key mediators.

The compounds of the invention also suppress inflammation and pyrexia due to cytokines and are, therefore, useful in the treatment of inflammation and cytokine-mediated chronic tissue degeneration which occurs in diseases such as rheumatoid or osteo-arthritis.

5 The over-production of cytokines such as TNF in bacterial, fungal or viral infections or in diseases such as cancer, leads to cachexia and muscle wasting. Compounds of the invention ameliorate these symptoms as well.

 The compounds of the invention elevate cAMP in certain areas of the brain and thereby counteract depression and memory impairment.

10 Compounds of the invention suppress cell proliferation in certain tumour cells and can be used, therefore, to prevent tumour growth and invasion of normal tissues.

 For the prophylaxis or treatment of disease the compounds may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

 For the treatment or prevention of any of the diseases or conditions described herein, the compounds of formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

 The term parenteral as used herein includes subcutaneous, intradermal, intravenous, intramuscular and intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compounds of the invention are useful for the treatment of humans.

 Oral pharmaceutical compositions containing the active ingredient are typically in the form of tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; 5 granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For 10 example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

In hard gelatin capsules, the active ingredient is typically mixed with 15 an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. In soft gelatin capsules, the active ingredient is typically mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are 20 suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of 25 ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous 30 suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut 35 oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a

thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

5 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example
10 sweetening, flavoring and coloring agents, may also be present.

 The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oil phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for
15 example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

 Syrups and elixirs may be formulated with sweetening agents, for
20 example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

 The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and
25 suspending agents which have been mentioned above.

 The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride
30 solution.

 In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides.

 In addition, fatty acids such as oleic acid find use in the preparation of
35 injectables.

Compounds of formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at normal body temperature and will therefore melt to
5 release the drug. Examples of such materials include cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, containing the compound of Formula I are employed. (For purposes of this application, topical application also includes mouth washes and gargles.)

10 Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about
15 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may contain from about 0.5 mg to about 5 g of
20 active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1 mg to about 500 mg of the active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg.

25 It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the invention can be synthesized using the general
30 synthesis schemes provided below. It will be apparent to one skilled in the art that similar methodology could be used to prepare the enantiomers or the racemates of the illustrated compounds.

The following abbreviations have the indicated meanings:

Ac	=	acetyl
Bn	=	benzyl
cAMP		cyclic adenosine-3',5'-monophosphate
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	=	diisobutylaluminum hydride
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
Et ₃ N	=	triethylamine
GST		glutathione transferase
HMDS		hexamethyldisilazide
LDA	=	lithium diisopropylamide
m-CPBA	=	metachloroperbenzoic acid
MMPP	=	monoperoxyphthalic acid
MPPM	=	monoperoxyphthalic acid, magnesium salt 6H ₂ O
Ms	=	methanesulfonyl = mesyl = SO ₂ Me
MsO	=	methanesulfonate = mesylate
NSAID	=	non-steroidal anti-inflammatory drug
o-Tol	=	ortho-tolyl
OXONE®	=	2KHSO ₅ •KHSO ₄ •K ₂ SO ₄
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
PDE		phosphodiesterase
Ph	=	phenyl
Phe	=	benzenediyl
PMB	=	para-methoxybenzyl
Pye	=	pyridinediyl
r.t.	=	room temperature
rac.	=	racemic
SAM	=	aminosulfonyl or sulfonamide or SO ₂ NH ₂
SEM	=	2-(trimethylsilyl)ethoxymethoxy
SPA	=	scintillation proximity assay
TBAF	=	tetra-n-butylammonium fluoride
Th	=	2- or 3-thienyl

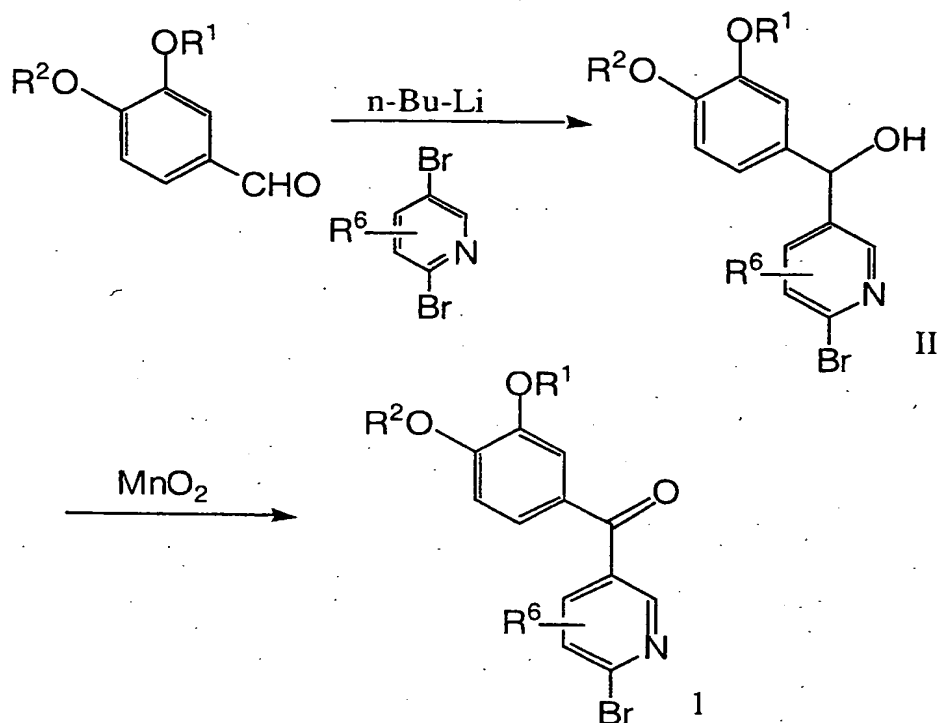
TFA	=	trifluoroacetic acid
TFAA	=	trifluoroacetic acid anhydride
THF	=	tetrahydrofuran
Thi	=	thiophenediyl
TLC	=	thin layer chromatography
TMS-CN	=	trimethylsilyl cyanide
TMSI		trimethylsilyl iodide
Tz	=	1H (or 2H)-tetrazol-5-yl
C ₃ H ₅	=	allyl

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

SCHEME 1

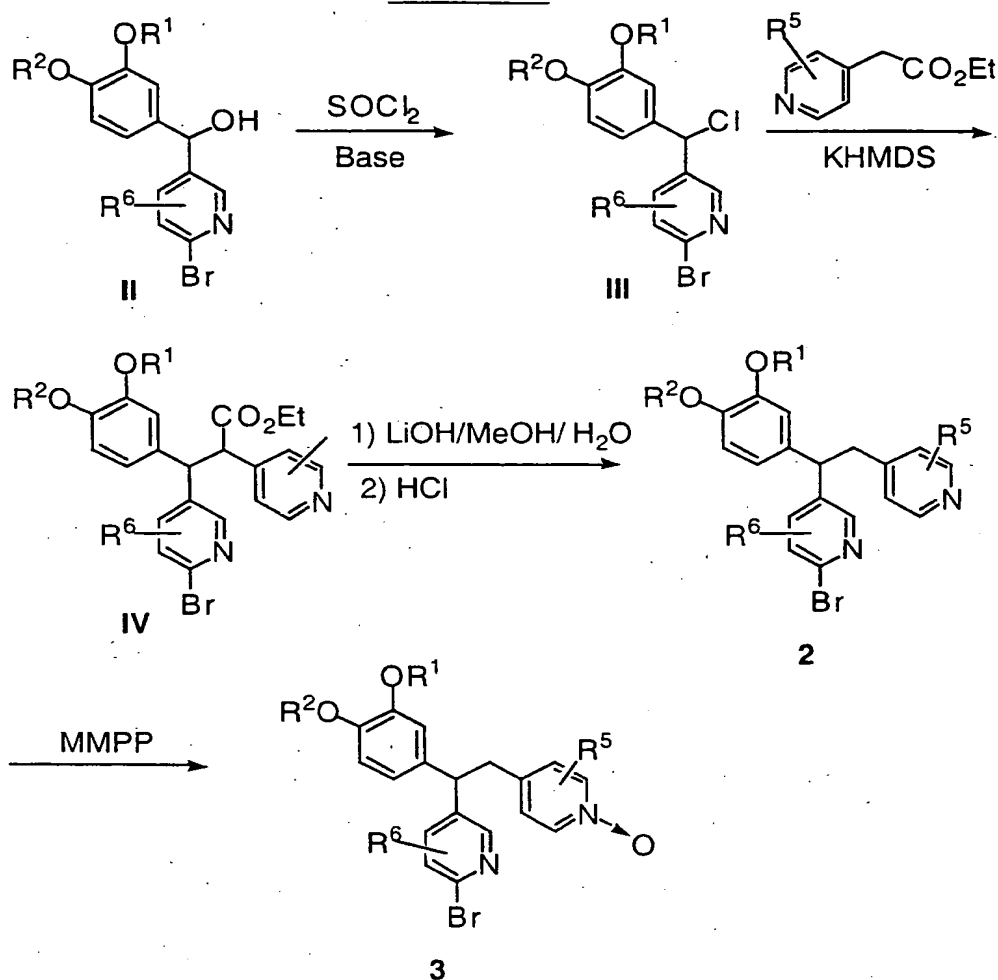
The preparation of bromopyridine intermediate 1 is shown in Scheme

- 5 1. Monolithiation of 2,5-dibromopyridine followed by the addition 3,4-bis(difluoromethoxy)benzaldehyde as found in U. S. Pat. No. 5,710,170 gave the secondary alcohol which was subsequently oxidized to the corresponding ketone with an oxidizing agent such as MnO₂.

SCHEME 1SCHEME 2

The preparation of bromopyridine intermediate 2 and 3 is shown in Scheme 2. The secondary alcohol II was converted to the corresponding chloride III using a chlorinating agent such as thionyl chloride in the presence of a base. This chloride was condensed with the α -anion of ethyl 4-pyridyl acetate, affording the ester IV which upon hydrolysis with a base such as lithium hydroxide, followed by acidification with an acid such as hydrochloric acid afforded the decarboxylated intermediate 2. Oxidation of the pyridine to the pyridine-N-oxide 3 was done with an oxidizing agent such as MMPP.

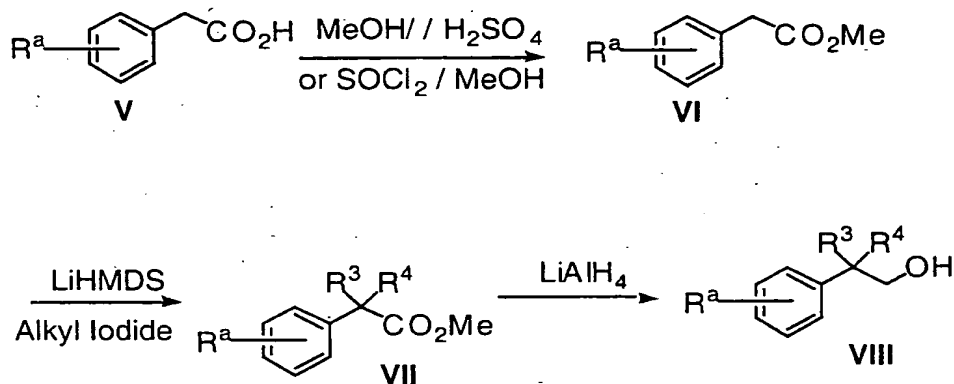
SCHEME 2



SCHEME 3

The general method for the preparation of substituted alcohols is presented in Scheme 3. Esterification of a suitable carboxylic acid V under Fisher's conditions followed by dialkylation of the methyl ester VI with a base such as LHMDS and a suitable alkylating agent, afforded the corresponding gem- α,α -disubstituted ester VII. This intermediate is converted to the alcohol VIII by reduction with a reducing agent such as lithium aluminum hydride.

SCHEME 3



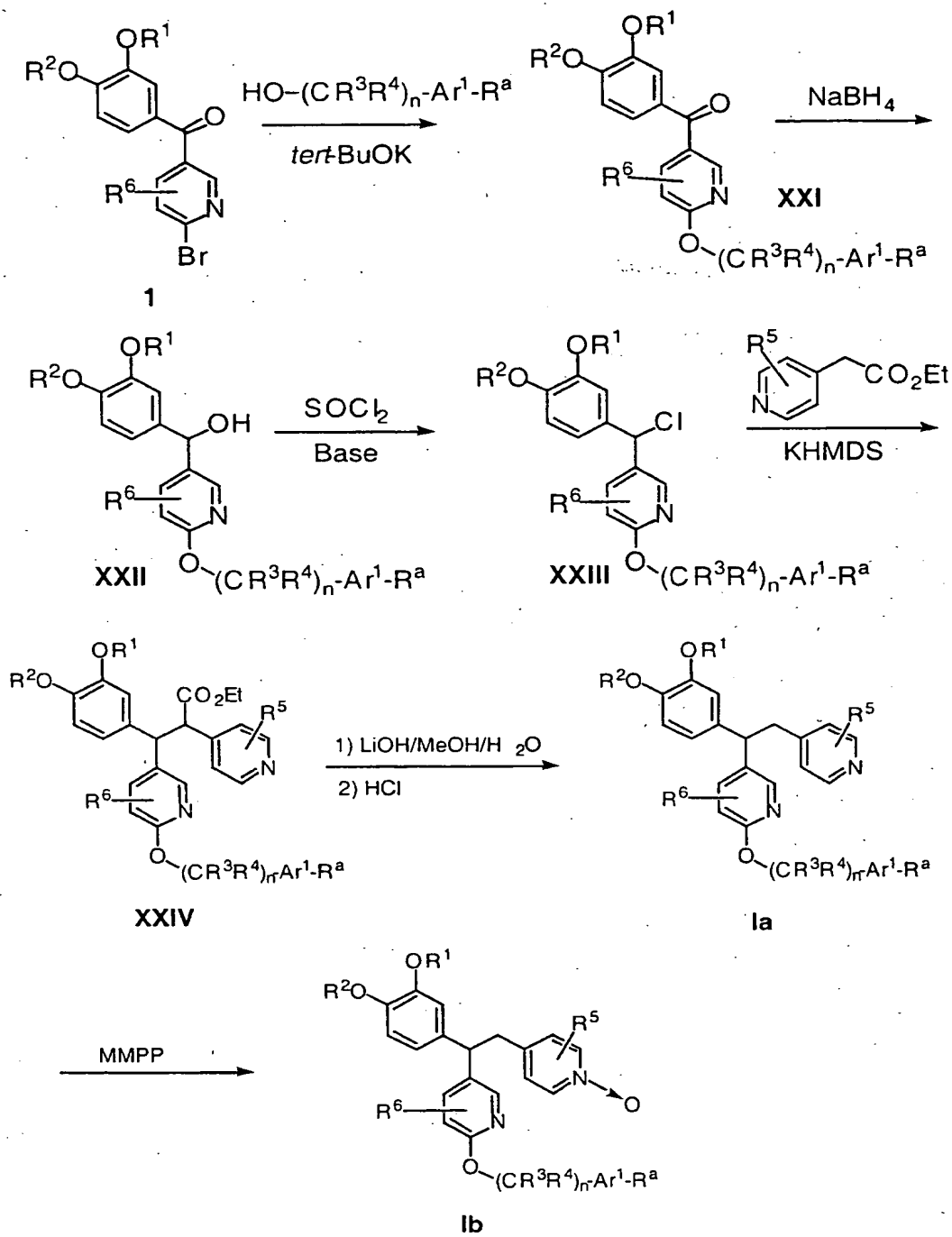
R^a represents a substituent group attached to Ar^1 , wherein Ar^1 represents phenyl. Up to 3 R^a groups may be present. The alkyl iodide provides the source for R^3 and R^4 , which can be the same or different.

5-

SCHEME 4

6-Oxy-3-pyridyl derivatives of formula Ia and Ib were prepared by the general method shown in Scheme 8. Bromopyridine 1 was coupled with a suitable alcohol in the presence of a base such as potassium tert-butoxide. The reduction of the ketone XXI was performed with a reducing agent such as sodium borohydride, followed by the conversion of the corresponding alcohol XXII to the chloride XXIII with a chlorinating agent such as thionyl chloride and a suitable base. This chloride was condensed with the α -anion of ethyl 4-pyridyl acetate, affording the ester XXIV which upon hydrolysis with a base such as lithium hydroxide, followed by acidification afforded the decarboxylated intermediate Ia. Oxidation of the pyridine to the pyridine-N-oxide Ib was done with an oxidizing agent such as MMPP. As noted above with respect to scheme 3, R^a represents a substituent group attached to Ar^1 and up to 3 R^a groups may be present.

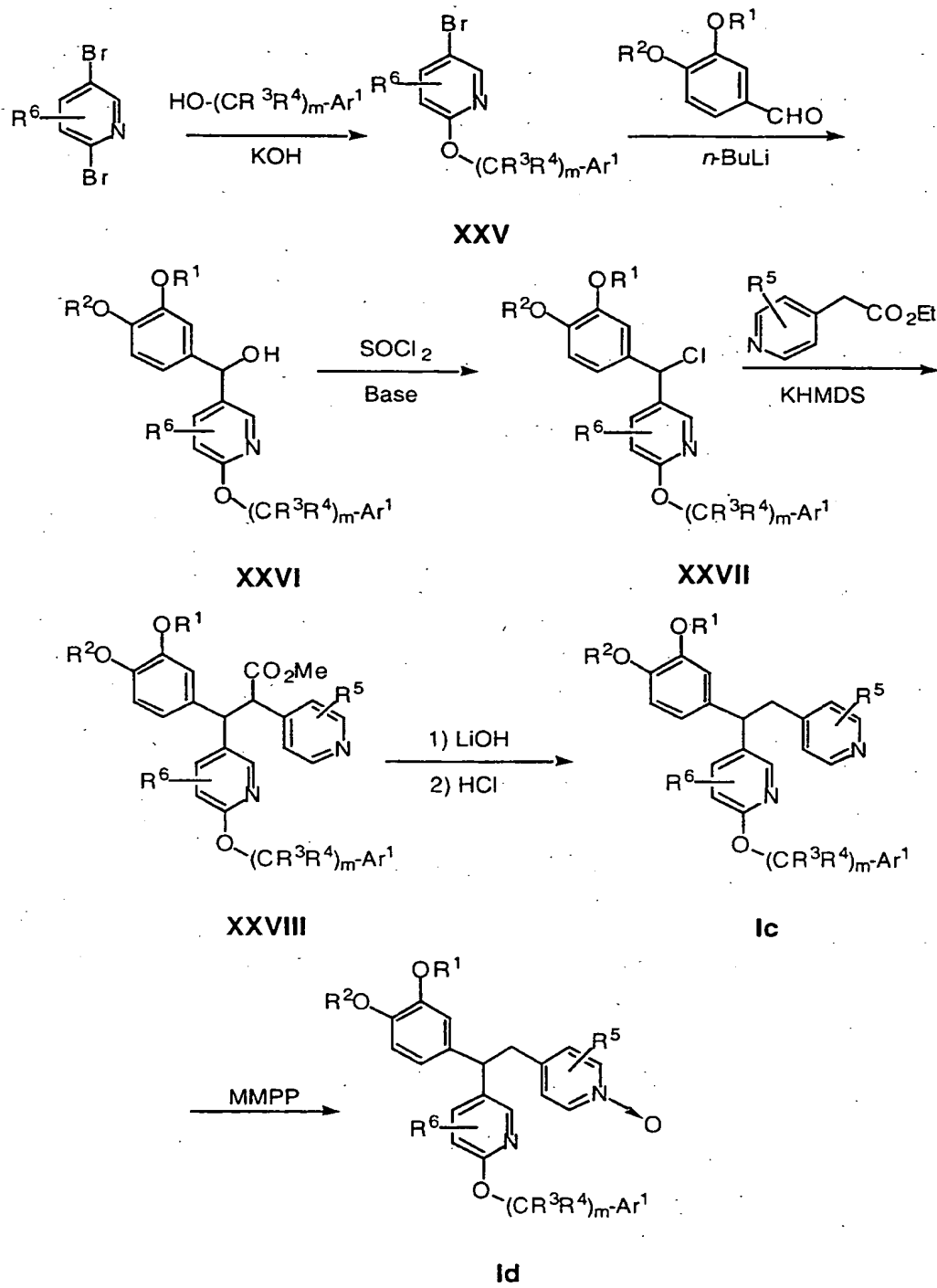
SCHEME 4



SCHEME 5

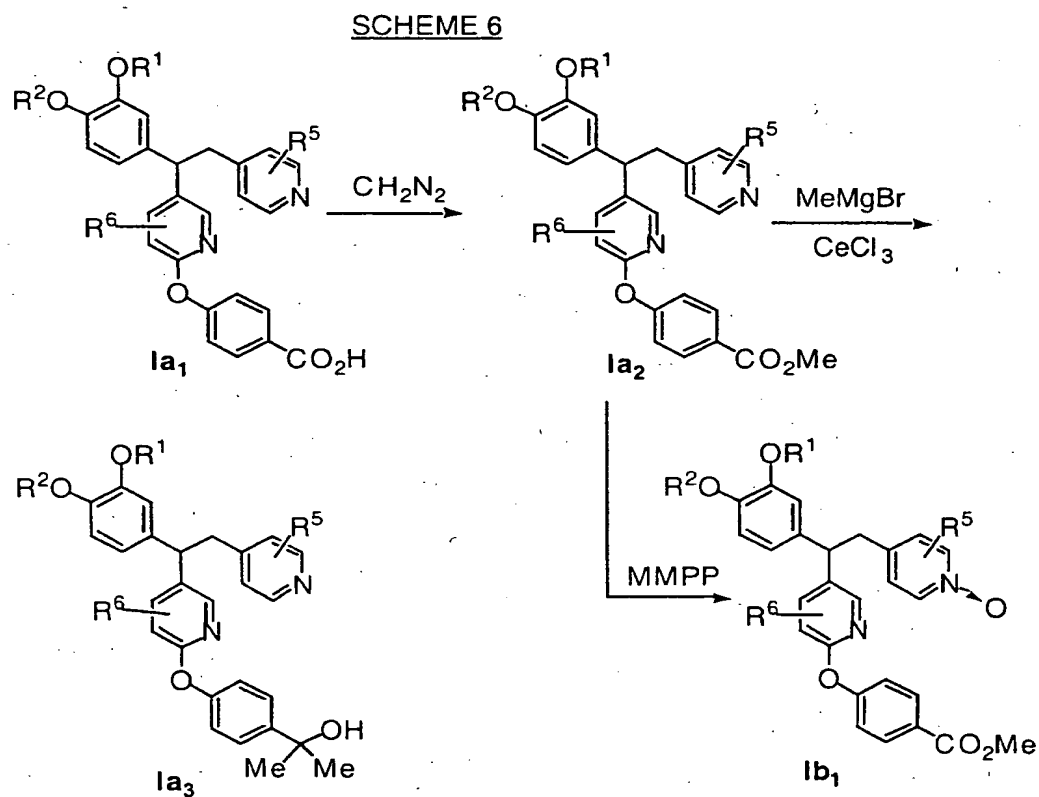
Alternatively, 6-Oxy-3-pyridyl derivatives of formula Ia and Ib were prepared by the general method shown in Scheme 9. 2,5-Dibromopyridine was coupled with a suitable alcohol in the presence of a base such as potassium hydroxide. Lithiation of the bromide XXV and condensation with 3,4-bis(substituted) benzaldehyde afforded the secondary alcohol XXVI which was converted to the corresponding chloride XXVII with a chlorinating agent such as thionyl chloride and a suitable base. This chloride was condensed with the α -anion of ethyl 4-pyridyl acetate, affording the ester XXVIII which upon hydrolysis with a base such as lithium hydroxide, followed by acidification with an acid such as HCl afforded the decarboxylated intermediate Ic. Oxidation of the pyridine to the pyridine-N-oxide Id was done with an oxidizing agent such as MMPP.

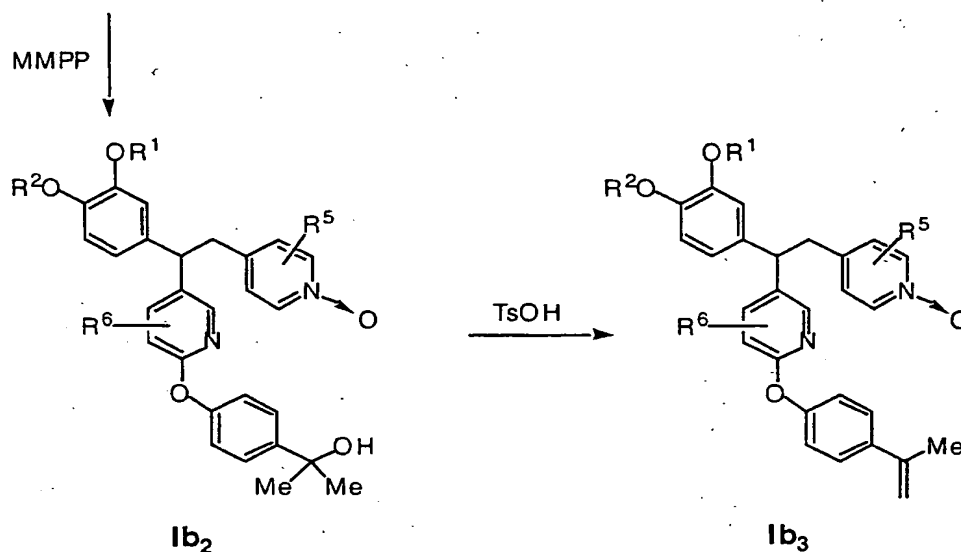
SCHEME 5



SCHEME 6

- 5 Scheme 6 describes the preparation of several derivatives from the same carboxylic acid Ia₁. Treatment of this acid with a methylating agent such as diazomethane afforded the corresponding ester Ia₂ which was derivatised to the pyridine-N-oxide Ib₁ in the presence of an oxidizing agent such as MMPP and to the tertiary alcohol Ia₃ by the addition of an organocerium reagent, such as generated by the reaction of MeMgBr and CeCl₃. This tertiary alcohol Ia₃ could then be oxidized to the corresponding pyridine-N-oxide Ib₂ which upon treatment with an acid such as p-toluenesulfonic acid afforded unsaturated derivative Ib₃.

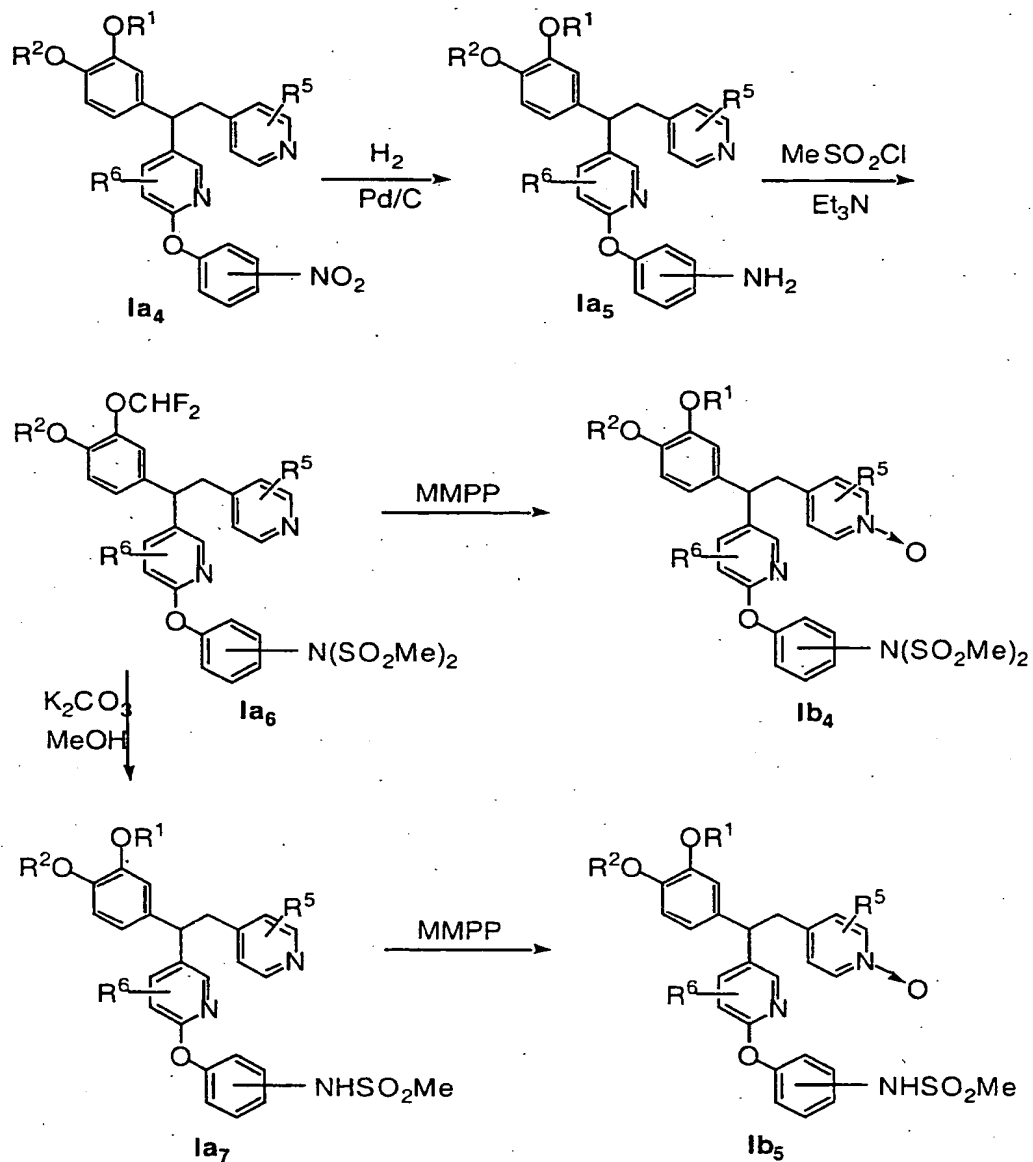




SCHEME 7

Mono and bis(methylsulfonamides) were prepared by the general
 method presented in Scheme 7. The nitroaryl derivative Ia₄ was provided according
 to Scheme 4. The pyridine bis-sulfonamide Ia₆ was obtained by reduction of the nitro
 group with a reducing agent such as Pd/C under an hydrogen atmosphere followed by
 sulfonylation of the corresponding amine Ia₅ in the presence of a sulfonylating agent
 such as methylsulfonyl chloride and a suitable base. This common intermediate could
 then be oxidized to the corresponding pyridine-N-oxide Ib₄ with an oxidizing agent
 such as MMPP or hydrolyzed under basic conditions to the mono-sulfonamide Ia₇
 followed by the oxidation to the pyridine-N-oxide with an oxidizing agent such as
 MMPP.

SCHEME 7



SCHEME 8

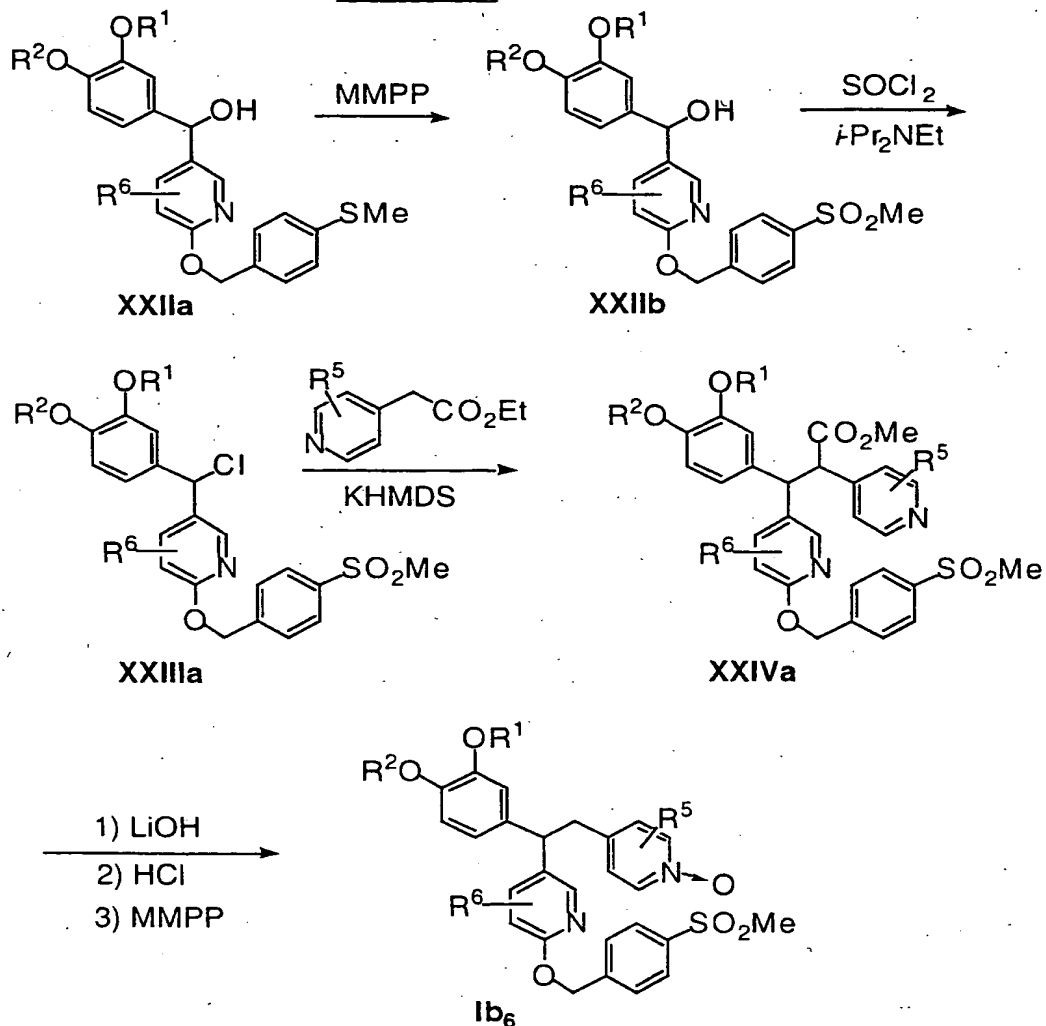
Methylsulfone **Ib₆** was prepared by the method presented in Scheme 8.

- 5 Thioether **XXIIa** was oxidized to the sulfone in the presence of an oxidizing agent such as MMPP followed by the conversion of the secondary alcohol to the corresponding chloride with a chlorination agent such as thionyl chloride and a base

such as Hunig's base. This chloride XXIIIa was condensed with the α -anion of ethyl 4-pyridyl acetate, affording the ester XXIVa which upon hydrolysis with a base such as lithium hydroxide, followed by acidification with an acid such as hydrochloric acid afforded the decarboxylated intermediate. Oxidation of the pyridine to the pyridine-

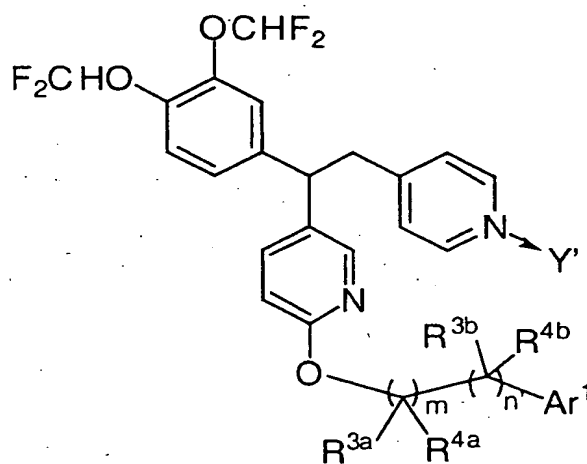
5 N-oxide Ib6 was done with an oxidizing agent such as MMPP.

SCHEME 8



Representative compounds of the invention are shown below.

TABLE 1



Ex ^a	Y'	m	R ^{3a}	R ^{4a}	n	R ^{3b}	R ^{4b}	Ar ¹
1	O	0	-	-	0	-	-	4-(trifluoromethoxy)phenyl
2	-	0	-	-	0	-	-	4-(methoxycarbonyl)phenyl
3	O	0	-	-	0	-	-	4-(methoxycarbonyl)phenyl
4	-	0	-	-	0	-	-	4-(2-hydroxypropan-2-yl)phenyl
5	O	0	-	-	0	-	-	4-(2-hydroxypropan-2-yl)phenyl
6	O	0	-	-	0	-	-	4-nitrophenyl
7	O	0	-	-	0	-	-	4-(methylsulphonylamino)phenyl
8	O	0	-	-	0	-	-	4-(trifluoromethyl)phenyl
9	O	0	-	-	0	-	-	3-(methylsulphonylamino)phenyl
10	O	0	-	-	0	-	-	4-(2-propenyl)phenyl
11	O	0	-	-	0	-	-	4-(2-propyl)phenyl
12	O	0	-	-	0	-	-	4-(dimethylsulphonylamino)phenyl

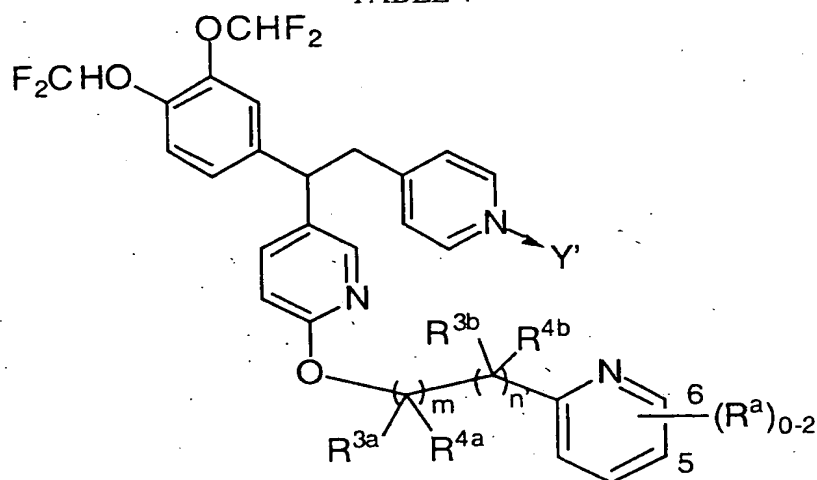
13 ^b	O	0	-	-	0	-	-	3-(hydroxymethyl)-4-(carboxyl)phenyl
14	O	1	H	H	0	-	-	phenyl
15	O	1	Me ^c	H	0	-	-	phenyl
16	O	1	H	H	0	-	-	3,4-difluorophenyl
17	O	1	H	H	0	-	-	4-(methylsulfonyl)phenyl
18 ^d	-	1	H	H	0	-	-	3,5-difluorophenyl
19 ^d	-	1	H	H	0	-	-	3,5-difluorophenyl
20 ^d	O	1	H	H	0	-	-	3,5-difluorophenyl
21 ^d	O	1	H	H	0	-	-	3,5-difluorophenyl
22	-	1	H	H	1	Me	Me	4-fluorophenyl
23	O	1	H	H	1	Me	Me	4-fluorophenyl
24	-	1	H	H	1	H	H	4-fluorophenyl
25	O	1	H	H	1	H	H	4-fluorophenyl
26	O	1	H	H	0	-	-	4-(trifluoromethyl)phenyl
27	O	1	H	H	0	-	-	4-(trifluoromethoxy)phenyl
28	O	1	Me	Me	1	H	H	phenyl
29	O	1	H	H	0	-	-	2-thienyl
30	-	1	Me	Me	0	-	-	4-fluorophenyl
31	O	1	Me	Me	0	-	-	4-fluorophenyl
32	O	1	H	H	0	-	-	4-fluorophenyl
33	O	1	H	H	0	-	-	4-chlorophenyl

^a Unless specified, all the compounds are racemic mixture. ^bSodium salt. ^cR, S mixture. ^dOptically pure.

	O	1	H	H	0	-	-	-
	O	1	Me	H	0	-	-	-
	O	1	H	H	0	-	-	4,5-difluoro
	O	1	H	H	0	-	-	4-(methylsulfonyl)
	-	1	H	H	0	-	-	3-fluoro
	-	1	H	H	0	-	-	4,5-difluoro
	O	1	H	H	0	-	-	4,5-dichloro
	O	1	H	H	0	-	-	5-fluoro
	-	1	H	H	1	Me	Me	4-fluoro
	O	1	H	H	1	Me	Me	4-fluoro
	-	1	H	H	1	H	H	5-fluoro
	O	1	H	H	1	H	H	4-fluoro
	O	1	H	H	0	-	-	4-(trifluoromethyl)
	O	1	H	H	0	-	-	4-(trifluoromethoxy)
	O	1	Me	Me	1	H	H	-
	O	1	H	H	0	-	-	-
	-	1	Me	Me	0	-	-	4-fluoro
	O	1	Me	Me	0	-	-	4-fluoro
	O	1	H	H	0	-	-	4-fluoro
	O	1	H	H	0	-	-	4-chloro

	O	1	H	H	0	-	-	-
	O	1	Me	H	0	-	-	-
	O	1	H	H	0	-	-	4,5-difluoro
	O	1	H	H	0	-	-	4-(methylsulfonyl)
	-	1	H	H	0	-	-	4,5-dichloro
	-	1	H	H	0	-	-	5-fluoro
	O	1	H	H	0	-	-	4,5-dichloro
	O	1	H	H	0	-	-	5-fluoro
	-	1	H	H	1	Me	Me	4-fluoro
	O	1	H	H	1	Me	Me	4-fluoro
	-	1	H	H	1	H	H	4-fluoro
	O	1	H	H	1	H	H	4-fluoro
	O	1	H	H	0	-	-	4-(trifluoromethyl)
	O	1	H	H	0	-	-	4-(trifluoromethoxy)
	O	1	Me	Me	1	H	H	-
	O	1	H	H	0	-	-	-
	-	1	Me	Me	0	-	-	4-fluoro
	O	1	Me	Me	0	-	-	4-fluoro
	O	1	H	H	0	-	-	4-fluoro
	O	1	H	H	0	-	-	4-chloro

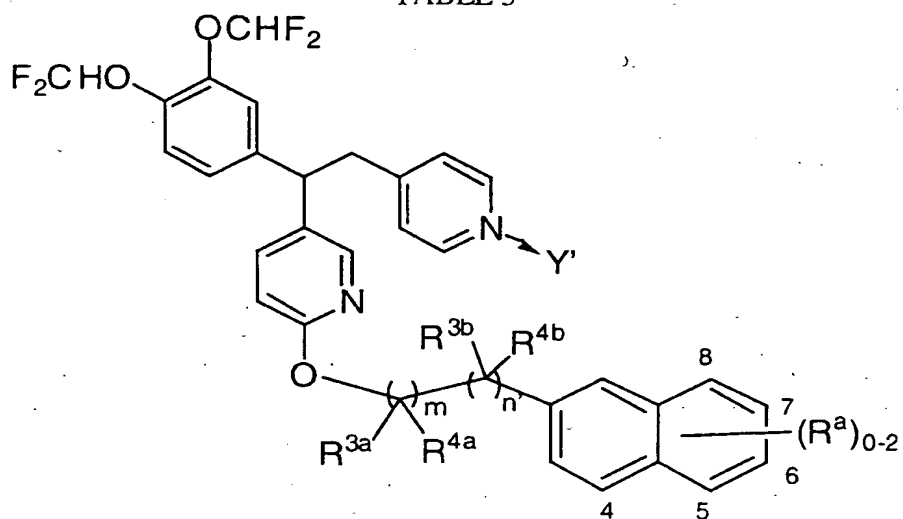
TABLE 4



Y'	m	R ^{3a}	R ^{4a}	n'	R ^{3b}	R ^{4b}	R ^a
O	0	-	-	0	-	-	6-(trifluoromethoxy)
-	0	-	-	0	-	-	6-(methoxycarbonyl)
O	0	-	-	0	-	-	6-(methoxycarbonyl)
-	0	-	-	0	-	-	6-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	6-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	6-nitro
O	0	-	-	0	-	-	6-(methylsulphonyl amino)
O	0	-	-	0	-	-	6-(trifluoromethyl)
O	0	-	-	0	-	-	5-(methylsulphonyl amino)
O	0	-	-	0	-	-	6-(2-propenyl)
O	0	-	-	0	-	-	6-(2-propyl)
O	0	-	-	0	-	-	6-(dimethylsulphonyl amino)
O	0	-	-	0	-	-	5-(hydroxymethyl)-6-(carboxyl)
O	1	H	H	0	-	-	-

O	1	Me	H	0	-	-	-
O	1	H	H	0	-	-	5,6-difluoro
O	1	H	H	0	-	-	6-(methylsulfonyl)
-	1	H	H	0	-	-	4,6-difluoro
-	1	H	H	0	-	-	5,6-dichloro
O	1	H	H	0	-	-	4,6-difluoro
O	1	H	H	0	-	-	5,6-dimethyl
-	1	H	H	1	Me	Me	6-fluoro
O	1	H	H	1	Me	Me	6-fluoro
-	1	H	H	1	H	H	6-fluoro
O	1	H	H	1	H	H	6-fluoro
O	1	H	H	0	-	-	6-(trifluoromethyl)
O	1	H	H	0	-	-	6-(trifluoromethoxy)
O	1	Me	Me	1	H	H	-
O	1	H	H	0	-	-	-
-	1	Me	Me	0	-	-	6-fluoro
O	1	Me	Me	0	-	-	6-fluoro
O	1	H	H	0	-	-	6-fluoro
O	1	H	H	0	-	-	6-fluoro

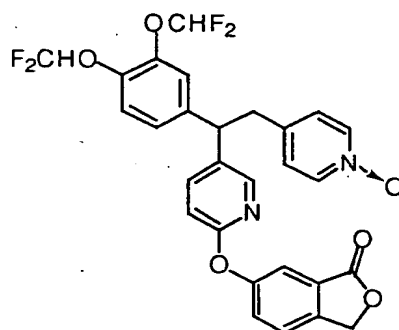
TABLE 5



Y'	m	R ^{3a}	R ^{4a}	n'	R ^{3b}	R ^{4b}	R ^a
O	0	-	-	0	-	-	7-(trifluoromethoxy)
-	0	-	-	0	-	-	7-(methoxycarbonyl)
O	0	-	-	0	-	-	7-(methoxycarbonyl)
-	0	-	-	0	-	-	7-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	7-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	7-nitro
O	0	-	-	0	-	-	7-(methylsulphonyl amino)
O	0	-	-	0	-	-	7-(trifluoromethyl)
O	0	-	-	0	-	-	6-(methylsulphonyl amino)
O	0	-	-	0	-	-	7-(2-propenyl)
O	0	-	-	0	-	-	7-(2-propyl)
O	0	-	-	0	-	-	7-(dimethylsulphonyl amino)
O	0	-	-	0	-	-	6-(hydroxymethyl)-7-(carboxyl)

O	1	H	H	0	-	-	-
O	1	Me	H	0	-	-	-
O	1	H	H	0	-	-	6,7-difluoro
O	1	H	H	0	-	-	7-(methylsulfonyl)
-	1	H	H	0	-	-	6,7-difluoro
-	1	H	H	0	-	-	5,7-difluoro
O	1	H	H	0	-	-	5-fluoro
O	1	H	H	0	-	-	6-fluoro
-	1	H	H	1	Me	Me	7-fluoro
O	1	H	H	1	Me	Me	7-fluoro
-	1	H	H	1	H	H	7-fluoro
O	1	H	H	1	H	H	7-fluoro
O	1	H	H	0	-	-	7-(trifluoromethyl)
O	1	H	H	0	-	-	7-(trifluoromethoxy)
O	1	Me	Me	1	H	H	-
O	1	H	H	0	-	-	-
-	1	Me	Me	0	-	-	7-fluoro
O	1	Me	Me	0	-	-	7-fluoro
O	1	H	H	0	-	-	7-fluoro
O	1	H	H	0	-	-	7-chloro

TABLE 6



Ex 34

TABLE 7 *IN VITRO* POTENCY OF SOME REPRESENTATIVE PDE 4 INHIBITORS.

Ex.	IC ₅₀ (nM) GST-Met 248 PDE 4a
1	2.85
16	1.43
23	3.2
28	0.2

5

ASSAYS DEMONSTRATING BIOLOGICAL ACTIVITY

LPS AND FMLP-INDUCED TNF- α AND LTB₄ ASSAYS IN HUMAN WHOLE BLOOD

10

Whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as PDE 4-selective inhibitors. Normal non-stimulated human blood does not contain detectable levels of TNF- α and LTB₄. Upon stimulation with LPS, activated monocytes express and secrete TNF- α up to 8 hours and plasma levels remain stable for 24 hours.

Published studies have shown that inhibition of TNF- α by increasing intracellular cAMP via PDE 4 inhibition and/or enhanced adenylyl cyclase activity occurs at the transcriptional level. LTB₄ synthesis is also sensitive to levels of intracellular cAMP and can be completely inhibited by PDE 4-selective inhibitors. As there is little LTB₄ produced during a 24 hour LPS stimulation of whole blood, an additional LPS stimulation followed by fMLP challenge of human whole blood is necessary for LTB₄ synthesis by activated neutrophils. Thus, using the same blood sample it is possible to evaluate the potency of a compound on two surrogate markers of PDE 4 activity in the whole blood.

- 10 Fresh blood was collected in heparinized tubes by venipuncture from healthy human volunteers (male and female). These subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 4 days prior to blood collection. Five hundred μ L aliquots of blood were pre-incubated with either 2 μ L of vehicle (DMSO) or 2 μ L test compound at varying concentrations for 15 minutes at 37°C. This was followed by the addition of either 10 μ L vehicle (PBS) as blanks or 10 μ L LPS (1 μ g/ml final concentration, Sigma Chem, #L-2630 from *E. coli*, serotype 0111:B4; diluted in 0.1% w/v BSA (in PBS)). After 24 hours of incubation at 37°C, another 10 μ L of PBS (blank) or 10 μ L of LPS (1 μ g/ml final concentration) was added to blood and incubated for 30 minutes at 37°C. The blood was then challenged with either 10 μ L of PBS (blank) or 10 μ L of fMLP (1 μ M final concentration, Sigma Chem #F-3506; diluted in 1% w/v BSA (in PBS)) for 15 minutes at 37°C. The blood samples were centrifuged at 1500xg for 10 minutes at 4°C to obtain plasma. A 50 μ L aliquot of plasma was mixed with 200 μ L methanol for protein precipitation and centrifuged as above. The supernatant was assayed for LTB₄ using an enzyme immunoassay kit (Cayman Chemicals #520111) according to the manufacturer's procedure. TNF- α was assayed in diluted plasma (in PBS) using an ELISA kit (Cistron Biotechnology) according to manufacturer's procedure.

ANTI-ALLERGIC ACTIVITY IN VIVO

- 30 Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitised guinea pigs. Guinea pigs were initially sensitised to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminium hydroxide and pertussis vaccine. Booster

doses of antigen were given two and four weeks later and at six weeks, animals were challenged with aerosolised ovalbumin whilst under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

SPA BASED PDE ACTIVITY ASSAY PROTOCOL

Compounds which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in 96-well plate format as follows:

In a 96 well-plate at 30°C was added the test compound (dissolved in 2 µl DMSO), 188 µl of substrate buffer containing [2,8-³H] adenosine 3',5'-cyclic phosphate (cAMP, 100 nM to 50 µM), 10 mM MgCl₂, 1 mM EDTA, 50 mM Tris, pH 7.5. The reaction was initiated by the addition of 10 µl of human recombinant PDE-IV (the amount was controlled so that ~10% product was formed in 10 min.). The reaction was stopped after 10 min. by the addition of 1 mg of PDE-SPA beads (Amersham). The product AMP generated was quantified on a Microbeta 96-well plate counter. The signal in the absence of enzyme was defined as the background. 100% activity was defined as the signal detected in the presence of enzyme and DMSO with the background subtracted. Percentage of inhibition was calculated accordingly. IC₅₀ value was approximated with a non-linear regression fit using the standard 4-parameter/multiple binding sites equation from a ten point titration.

IC₅₀ values shown in Table 7 were determined with 100 nM cAMP using the purified GST fusion protein of the human recombinant phosphodiesterase IVa (met-248) produced from a baculovirus/Sf-9 expression system.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C; the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations; the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; yields are given for illustration only; when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz, 400 MHz or 500 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal; chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

EXAMPLE 1

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[4-(TRIFLUOROMETHOXY)PHENOXY]-3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

Step 1

[3,4-Bis(difluoromethoxy)phenyl]-{6-[4-(trifluoromethoxy)phenoxy]-3-pyridyl}methanone

To a 0°C solution of 4-trifluoromethoxyphenol (0.33 mL, 2.54 mmol) in 5 mL of anhydrous DMF, was added dropwise 2.54 mL (2.54 mmol) of a 1.0 M solution of potassium t-butoxide in THF followed by 500 mg (1.27 mmol) of intermediate 1. The resulting orange solution was stirred 20 h at room temperature, quenched by the addition of a saturated aqueous NH₄Cl solution and diluted with Et₂O. The organic layer was washed with a 0.5 N NaOH solution, water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was

purified by flash chromatography on silica gel (10% Ethyl acetate/toluene) to afford the desired aryl ether as an oil (484 mg, 77 %).

Step 2

- 5 [3,4-Bis(difluoromethoxy)phenyl]-{6-[4-(trifluoromethoxy)phenoxy]-3-pyridyl}methanol

To a 0°C solution of ketone (484 mg, 0.985 mmol) from Step 1 above in 12 mL of a 5 : 1 mixture of THF : MeOH, was added slowly 75 mg (1.97 mmol) of NaBH₄. The resulting solution was stirred 2.5 h at 0 °C, quenched with a saturated aqueous NH₄Cl solution and diluted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was used directly for the next step without any purification.

Step 3

- 15 [3,4-Bis(difluoromethoxy)phenyl]-{6-[4-(trifluoromethoxy)phenoxy]-3-pyridyl}chloromethane

To a 0°C solution of alcohol (500 mg, 1.01 mmol) from Step 2 above and i-Pr₂N₂Et (400 mL, 2.22 mmol) in 14 mL of a 1:1 mixture of toluene:THF, was slowly added SOCl₂ (100 mL, 1.11 mmol). The resulting yellow solution was stirred 20 30 minutes at 0°C, quenched with water and diluted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was used directly for the next step without any purification.

Step 4

- 25 4-{1-Carbethoxy-2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-[4-(trifluoromethoxy)phenoxy]-3-pyridyl]ethyl}pyridine

To a solution of ethyl 4-pyridyl acetate (502 mg, 3.03 mmol) and HMPA (530 mL, 3.03 mmol) in 12 mL of THF, was slowly added 6.1 mL (3.03 mmol) of a 0.5 M solution of KHMDS in toluene. The resulting cloudy orange solution was stirred 10 minutes at room temperature followed by the addition of a THF (6 mL) solution of the crude chloride from Step 3 above. The resulting mixture was stirred 30 minutes at room temperature, quenched with a saturated aqueous NH₄Cl solution and diluted with ethyl acetate. The organic layer was washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was used directly for the next step without any purification.

Step 5

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-{6-[4-(trifluoromethoxy)phenoxy]-3-pyridyl}ethyl}pyridine

- 5 To a solution of the crude ester from Step 4 above in 25 mL of a 3:1:1 mixture of THF:MeOH:water, was added 5.1 mL (10.3 mmol) of a 2 N solution of LiOH. The resulting solution was stirred at 65 °C for 1.5 h, cooled down to room temperature followed by the addition of 10 mL of a 1.0 N HCl solution. The resulting mixture was rotovaped down to evaporate MeOH and the aqueous residue was diluted
- 10 with ethyl acetate. The organic layer was washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (50% Ethyl acetate/hexane) to afford the desired pyridine as an oil (380 mg, 68 % from Step 2).

15 Step 6

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-{6-[4-(trifluoromethoxy)phenoxy]-3-pyridyl}ethyl}pyridine-N-oxide

- To a solution of 4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-{6-[4-(trifluoromethoxy)phenoxy]-3-pyridyl}ethyl}pyridine (340 mg, 0.598 mmol) from
- 20 Step 5 above in a mixture of 6 mL of CH₂Cl₂ and 0.6 mL of MeOH, was added MMPP (222 mg, 0.359 mmol) in one portion. The mixture was stirred 24 h at room temperature and the reaction was completed with an other 50 mg of MMPP. The reaction was quenched with a saturated aqueous NaHCO₃ solution and diluted with CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄ and
- 25 concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% MeOH/CH₂Cl₂) to afford the title compound as an amorphous solid (340 mg, 97 %).

- ¹H NMR (500 MHz, Acetone-d₆) δ 8.10 (d, 1H), 7.94 (m, 2H), 7.89 (m, 1H), 7.41 (s, 1H), 7.36-7.33 (d, 2H), 7.28 (d, 1H), 7.23-7.18 (m, 4H), 6.98 (d,
- 30 1H), 6.95 (t, 1H), 6.93 (t, 1H), 4.56 (t, 1H), 3.49 (m, 2H).

EXAMPLE 2

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-{6-[4-(METHOXYCARBONYL)PHENOXY]-3-PYRIDYL}ETHYL}PYRIDINE

35 Step 1

[3,4-Bis(difluoromethoxy)phenyl]-{6-[4-(methoxycarbonyl)phenoxy]-3-pyridyl}methanone

To a 0°C solution of intermediate 1 (507 mg, 1.29 mmol) and 4-methoxycarbonylphenol (391 mg, 2.6 mmol) in 5 mL of anhydrous DMF, was added dropwise 2.6 mL (2.6 mmol) of a 1.0 M solution of potassium *t*-butoxide. The resulting orange solution was stirred 15 h at room temperature, quenched by the addition of a saturated aqueous NH₄Cl solution and diluted with Et₂O. The organic layer was washed with 0.1 N NaOH solution, water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was used directly for the next step without any purification.

Step 2

[3,4-Bis(difluoromethoxy)phenyl]-{6-[4-(methoxycarbonyl)phenoxy]-3-pyridyl}methanol

To a 0°C solution of ketone (540 mg, 1.16 mmol) from Step 1 in 12 mL of a 5 : 1 mixture of THF : MeOH, was added slowly 88 mg (2.3 mmol) of NaBH₄. The resulting solution was stirred 30 minutes at 0 °C, quenched with a saturated aqueous NH₄Cl solution and diluted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was used directly for the next step without any purification.

Step 3

[3,4-Bis(difluoromethoxy)phenyl]-{6-[4-(methoxycarbonyl)phenoxy]-3-pyridyl}chloromethane

To a 0 °C solution of alcohol (535 mg, 1.14 mmol) from step 2 and *i*-Pr₂NEt (436 mL, 2.5 mmol) in 10 mL of anhydrous toluene, was slowly added SOCl₂ (145 mL, 2.0 mmol). The resulting yellow solution was stirred 30 minutes at 0 °C, 10 minutes at room temperature, quenched with water and diluted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was used directly for the next step without any purification.

Step 4

4-{1-Carbethoxy-2-[3,4-bis(difluoromethoxy)phenyl]-2-{6-[4-(methoxycarbonyl)phenoxy]-3-pyridyl}ethyl}pyridine

To a solution of ethyl 4-pyridyl acetate (564 mg, 3.42 mmol) and HMPA (594 mL, 3.42 mmol) in THF, was slowly added 6.8 mL (3.42 mmol) of a 0.5 M solution of KHMDS in toluene. The resulting cloudy orange solution was stirred 10 minutes at room temperature followed by the addition of a THF (8 mL) solution of the crude chloride from Step 3. The resulting mixture was stirred 30 minutes at room temperature, quenched with a saturated aqueous NH₄Cl solution and diluted with ethyl acetate. The organic layer was washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was used directly for the next step without any purification.

Step 5

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-{6-[4-(methoxycarbonyl)phenoxy]-3-pyridyl}ethyl}pyridine

To a solution of the crude ester from Step 4 above in 25 mL of a 3 : 1 : 1 mixture of THF : MeOH : water, was added 5.1 mL (10.3 mmol) of a 2 N solution of LiOH. The resulting solution was stirred at 65 °C for 1.5 h, cooled down to room temperature followed by the addition of 11 mL of a 1.0 N HCl solution. The resulting mixture was rotovaped down to evaporate MeOH and the aqueous residue was diluted with ethyl acetate. The organic layer was washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and treated with CH₂N₂ and monitored by TLC until all the carboxylic acid have been esterified. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (70% Ethyl acetate/hexane) to afford the title compound as a viscous oil (432 mg, 62 % from Step 1).

¹H NMR (300 MHz, Acetone-d₆) δ 8.38 (d, 2H), 8.14 (d, 1H), 8.05-7.99 (m, 2H), 7.93 (dd, 1H), 7.43 (d, 1H), 7.36 (dd, 1H), 7.28 (d, 1H), 7.22-7.14 (m, 4H), 7.01 (d, 1H), 6.96 (t, 1H), 6.94 (t, 1H), 4.63 (t, 1H), 3.87 (s, 3H), 3.50 (d, 2H).

EXAMPLE 3

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[4-(METHOXYCARBONYL)PHENOXY]-3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

5 To a solution of 4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-[4-(methoxycarbonyl)phenoxy]-3-pyridyl]ethyl}pyridine from Example 1 (249 mg, 0.46 mmol) in a mixture of 5 mL of CH₂Cl₂ and 0.5 mL of MeOH, was added MMPP (171 mg, 0.28 mmol) in one portion. The mixture was stirred 24 h at room temperature, quenched with a saturated aqueous NaHCO₃ solution and diluted with
10 CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Gradient 20% to 40% EtOH/ethyl acetate) to afford the title compound as a viscous oil (260 mg, 71 %).

¹H NMR (400 MHz, Acetone-d₆) δ 8.15 (d, 1H), 8.05-8.01 (m, 2H),
15 7.98-7.92 (m, 3H), 7.44 (d, 1H), 7.36 (dd, 1H), 7.29 (d, 1H), 7.23-7.16 (m, 4H), 7.03 (d, 1H), 6.97 (t, 1H), 6.94 (t, 1H), 4.60 (t, 1H), 3.89 (s, 3H), 3.50 (dd, 2H).

EXAMPLE 4

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[4-(2-HYDROXYPROPAN-2-YL)PHENOXY]-3-PYRIDYL]ETHYL}PYRIDINE

20 A suspension of dry CeCl₃ (2.7 g, 11.0 mmol) in 50 mL of THF was refluxed 1 h, cooled to 0 °C and treated with 3.7 mL (11.0 mmol) of a 3.0 M solution of MeMgBr in Et₂O. The resulting mixture was stirred 1 h at 0 °C, cooled to -40 °C followed by the addition of a THF (10 mL) solution of 4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-[4-(methoxycarbonyl)phenoxy]-3-pyridyl]ethyl}pyridine. After stirring 30 minutes at -40 °C, the reaction was quenched
25 with a saturated aqueous NH₄Cl solution and diluted with ethyl acetate. The organic layer was washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel
30 (Gradient 5% to 10% EtOH/ethyl acetate) to afford the title compound as a foam (1.1 g, 99 %).

¹H NMR (300 MHz, Acetone-d₆) δ 8.38 (s, 2H), 8.07 (d, 1H), 7.84 (dd, 1H), 7.55-7.49 (m, 2H), 7.40 (s, 1H), 7.34 (dd, 1H), 7.26 (d, 1H), 7.22-7.16 (m, 2H), 7.03-

6.96 (m, 2H), 6.94 (t, 1H), 6.93 (t, 1H), 6.88 (d, 1H), 4.59 (t, 1H), 4.00 (s, 1H), 3.50 (d, 2H), 1.50 (s, 6H).

EXAMPLE 5

5 4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-{6-[4-(2-HYDROXYPROPAN-2-YL)PHENOXY]-3-PYRIDYL}ETHYL}PYRIDINE-N-OXIDE

Following the procedure described in Example 3 but using 4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-{6-[4-(2-hydroxypropan-2-yl)phenoxy]-3-pyridyl}ethyl}pyridine as starting material, the title compound was obtained as a
10 white foam (23 mg, 77%).

¹H NMR (400 MHz, Acetone-d₆) δ 8.08 (d, 1H), 7.98-7.94 (m, 2H), 7.85 (dd, 1H), 7.55-7.50 (m, 2H), 7.42 (s, 1H), 7.35 (dd, 1H), 7.27 (d, 1H), 7.21 (d, 2H), 7.03-6.97 (m, 2H), 6.96 (t, 1H), 6.94 (t, 1H), 6.90 (d, 1H), 4.55 (t, 1H), 3.50 (d, 2H), 1.51 (s, 6H).

15

EXAMPLE 6

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(4-NITROPHENOXY)-3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

20

Step 1

[3,4-Bis(difluoromethoxy)phenyl]-[6-(4-nitrophenoxy)-3-pyridyl]methanone

Following the procedure described in Example 1, Step 1 but substituting 4-nitrophenol for 4-trifluoromethoxyphenol, the desired aryl ether was
25 obtained as an oil (1.02 mg, 89 %).

Step 2

[3,4-Bis(difluoromethoxy)phenyl]-[6-(4-nitrophenoxy)-3-pyridyl]methanol

The procedure for the reduction of the ketone described in Example 1,
30 Step 2 was applied using the product of step 1 above as starting material. The alcohol obtained was used directly for the next step without any purification.

Step 3

[3,4-Bis(difluoromethoxy)phenyl]-[6-(4-nitrophenoxy)-3-pyridyl]chloromethane

The procedure for the formation of the chloride described in Example 1, Step 3 was applied using the product of Step 2 above as starting material. The chloride obtained was used directly for the next step without any purification.

5 Step 4

4-{1-Carbethoxy-2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-(4-nitrophenoxy)-3-pyridyl]ethyl}pyridine

The procedure for the alkylation with ethyl 4-pyridylacetate described in Example 1, Step 4 was applied using the product of Step 3 above as starting material. The ethyl ester obtained was used directly for the next step without any purification.

Step 5

15 4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-(4-nitrophenoxy)-3-pyridyl]ethyl}pyridine

The procedure for the hydrolysis/decarboxylation described in Example 1, Step 5 was applied using the product of Step 4 above as starting material. The protected aminopyridine was obtained as an oil (710 mg, 60% for 4 steps).

20 Step 6

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-nitrophenoxy)-3-pyridyl]ethyl}pyridine-N-oxide

The procedure for the oxidation of the pyridine group described in Example 1, Step 6 was applied using the product of Step 5 above as starting material.

25 The title compound was obtained as an oil (103 mg, 91%).

¹H NMR (500 MHz, Acetone-d₆) δ 8.27 (d, 2H), 8.19 (s, 1H), 7.99-7.94 (m, 3H), 7.44 (s, 1H), 7.38-7.19 (m, 4H), 7.10 (d, 2H), 6.96 (t, 1H), 6.94 (t, 1H), 4.60 (t, 1H), 3.51 (m, 2H).

EXAMPLE 7

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[4-(METHYLSULFONYLAMINO)PHENOXY]-3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

5

Step 1

4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-(4-aminophenoxy)-3-pyridyl]ethyl}pyridine

To a solution of 4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-(4-nitrophenoxy)-3-pyridyl]ethyl}pyridine (600 mg, 1.13 mmol) from Example 6, Step 5 in 20 mL EtOH, was added 120 mg of Pd/C 10% and the resulting mixture was stirred 20 h under H₂ atmosphere. The reaction was filtered on celite, washed with ethyl acetate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOH/Ethyl acetate) to afford the amine as an oil (500 mg, 88%).

15

Step 2

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(methylsulfonylamino)phenoxy]-3-pyridyl]ethyl}pyridine

To a 0 °C solution of amine from Step 1 above (200 mg, 0.4 mmol) in 6 mL of CH₂Cl₂ was added 0.28 mL (2.0 mmol) of Et₃N followed by 0.11 mL (1.4 mmol) of methylsulfonyl chloride. The solution was stirred at 0 °C for 1.5 h, quenched with water and diluted with CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in 10 mL of a 1:1:1 mixture of THF:MeOH:1 N K₂CO₃, stirred for 3.5 h at room temperature, quenched with a saturated aqueous NH₄Cl solution and diluted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (100% ethyl acetate) to afford the methyl sulfonamide as a foam (114 mg, 51 %).

20
25
30

Step 3

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(methylsulfonylamino)phenoxy]-3-pyridyl]ethyl}pyridine-N-oxide

The procedure for the oxidation of the pyridine group described in Example 1, Step 6 was applied using the product of Step 2 above as starting material. The title compound was obtained as a foam (85 mg, 73%).

¹H NMR (500 MHz, Acetone-d₆) δ 8.71 (brs, 1H), 8.08 (d, 1H), 7.97 (d, 2H), 7.85 (dd, 1H), 7.41 (d, 1H), 7.37-7.33 (m, 3H), 7.28 (d, 1H), 7.20 (d, 2H), 7.10-6.78 (m, 5H), 4.54 (t, 1H), 3.49 (m, 2H), 2.97 (s, 3H).

EXAMPLE 8

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-{6-[4-(TRIFLUOROMETHYL)PHENOXY]-3-PYRIDYL}ETHYL}PYRIDINE-N-OXIDE

Following the procedure described in Example 1 but substituting 4-trifluoromethylphenol for 4-trifluoromethoxyphenol, the title compound was obtained as a white foam (270 mg).

¹H NMR (500 MHz, Acetone-d₆) δ 8.14 (d, 1H), 7.98-7.92 (m, 3H), 7.73 (d, 2H), 7.43 (d, 1H), 7.35 (dd, 1H), 7.29 (m, 3H), 7.19 (d, 2H), 7.03 (d, 1H), 6.96 (t, 1H), 6.94 (t, 1H), 4.58 (t, 1H), 3.50 (m, 2H).

EXAMPLE 9

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-{6-[3-(METHYLSULFONYLAMINO)PHENOXY]-3-PYRIDYL}ETHYL}PYRIDINE-N-OXIDE

Following the procedure described in Example 1, Step 1 but substituting 3-nitrophenol for 4-trifluoromethoxyphenol, the desired aryl ether was obtained as an oil (1.06 g, 92%).

25

Step 2

[3,4-Bis(difluoromethoxy)phenyl]-[6-(3-nitrophenoxy)-3-pyridyl]methanol

The procedure for the reduction of the ketone described in Example 1, Step 2 was applied using the product of Step 1 above as starting material. The alcohol obtained was used directly for the next step without any purification.

30

Step 3

[3,4-Bis(difluoromethoxy)phenyl]-[6-(3-nitrophenoxy)-3-pyridyl]chloromethane

The procedure for the formation of the chloride described in Example 1, Step 3 was applied using the product of Step 2 above as starting material. The chloride obtained was used directly for the next step without any purification.

Step 4

4-{1-Carbethoxy-2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-(3-nitrophenoxy)-3-pyridyl]ethyl}pyridine

The procedure for the alkylation with ethyl 4-pyridylacetate described in Example 1, Step 4 was applied using the product of Step 3 above as starting material. The ethyl ester obtained was used directly for the next step without any purification.

Step 5

4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-(4-nitrophenoxy)-3-pyridyl]ethyl}pyridine

The procedure for the hydrolysis/decarboxylation described in Example 1, Step 5 was applied using the product of Step 4 above as starting material. The protected aminopyridine was obtained as an oil (410 mg, 34% for 4 steps).

Step 6

4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-(4-aminophenoxy)-3-pyridyl]ethyl}pyridine

The procedure for the reduction of the nitro group described in Example 7, Step 1 was applied using the product of Step 5 above as starting material. The amine was obtained as an oil (185 mg, 48%).

Step 7

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[3-(methylsulfonylamino)phenoxy]-3-pyridyl]ethyl}pyridine

The procedure for the sulfonylation of the amine group described in Example 7, Step 2 was applied using the product of Step 6 above as starting material. The sulfonamide was obtained as an oil (80 mg, 37%).

Step 8

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-{6-[3-(methylsulfonylamino)phenoxy]-3-pyridyl}ethyl}pyridine-N-oxide

The procedure for the oxidation of the pyridine group described in Example 1, Step 6 was applied using the product of Step 7 above as starting material. The title compound was obtained as a foam (55 mg, 67%).

¹H NMR (500 MHz, Acetone-d₆) δ 9.04 (brs, 1H), 8.21 (d, 1H), 8.10 (d, 2H), 7.98 (dd, 1H), 7.54 (s, 1H), 7.46 (m, 3H), 7.40 (d, 1H), 7.31 (d, 2H), 7.25 (dd, 1H), 7.22-6.90 (m, 5H), 4.67 (t, 1H), 3.61 (m, 2H), 3.12 (s, 3H).

10

EXAMPLE 10

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-{6-[4-(2-PROPENYL)PHENOXY]-3-PYRIDYL}ETHYL}PYRIDINE-N-OXIDE

To a solution of 148 mg (0.26 mmol) of 4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-{6-[4-(2-hydroxypropan-2-yl)phenoxy]-3-pyridyl}ethyl}pyridine-N-oxide (Example 5) in 3.0 mL of CH₂Cl₂ was added 85 mg (0.45 mmol) of *p*-toluenesulfonic acid at room temperature. The solution was stirred 2 days at room temperature, quenched with a saturated aqueous NaHCO₃ solution and diluted with CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Gradient 20% to 30% EtOH/ethyl acetate) to afford the title compound as a foam (98 mg, 68 %).

¹H NMR (500 MHz, Acetone-d₆) δ 8.09 (d, 1H), 7.95 (d, 2H), 7.86 (dd, 1H), 7.54-7.50 (m, 2H), 7.41 (s, 1H), 7.34 (dd, 1H), 7.27 (d, 1H), 7.18 (d, 2H), 7.06-7.03 (m, 2H), 6.95 (t, 1H), 6.93 (t, 1H), 6.93 (d, 1H), 5.38 (s, 1H), 5.07 (s, 1H), 4.55 (t, 1H), 3.5 (dd, 2H), 2.12 (s, 3H).

25

EXAMPLE 11

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-{6-[4-(2-PROPYL)PHENOXY]-3-PYRIDYL}ETHYL}PYRIDINE-N-OXIDE

30

Following the procedure described in Example 1 but substituting 4-(2-propyl)phenol for 4-trifluoromethoxyphenol, the title compound was obtained as a white foam (233 mg).

¹H NMR (300 MHz, Acetone-d₆) δ 8.08 (d, 1H), 7.95 (m, 2H), 7.83 (dd, 1H), 7.41 (d, 1H), 7.35-6.69 (m, 11H), 4.53 (t, 1H), 3.48 (m, 2H), 2.90 (m, 1H), 1.23 (d, 3H).

5

EXAMPLE 12

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-{6-[4-(DIMETHYLSULFONYLAMINO)PHENOXY]-3-PYRIDYL}ETHYL}PYRIDINE-N-OXIDE

Step 1

10 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-{6-[4-(dimethylsulfonylamino)phenoxy]-3-pyridyl}ethyl}pyridine

To a 0 °C solution of 4-{2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-(4-aminophenoxy)-3-pyridyl]ethyl}pyridine from Example 7, Step 1 (817 mg, 1.64 mmol) in 25 mL of CH₂Cl₂, was added 1.1 mL (8.2 mmol) of Et₃N followed by 0.44 mL (5.74 mmol) of methylsulfonyl chloride. The resulting solution was stirred 1 h at 0 °C, quenched with water and diluted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (100% Ethyl acetate) to afford the disulfonamide as an amorphous solid (807 mg, 75 %).

20

Step 2

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-{6-[4-(dimethylsulfonylamino)phenoxy]-3-pyridyl}ethyl}pyridine-N-oxide

The procedure for the oxidation of the pyridine group described in Example 1, Step 6 was applied using the product of Step 1 above as starting material. The title compound was obtained as a foam (725 mg, 88%).

¹H NMR (500 MHz, Acetone-d₆) δ 8.13 (d, 1H), 7.94 (d, 2H), 7.90 (dd, 1H), 7.50 (m, 2H), 7.42 (d, 1H), 7.34 (m, 1H), 7.28 (d, 1H), 7.20-7.16 (m, 4H), 7.00 (d, 1H), 6.96 (t, 1H), 6.93 (t, 1H), 4.57 (t, 1H), 3.49 (m, 2H), 3.48 (s, 6H).

30

EXAMPLE 13

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[(4-HYDROXYMETHYL-
3-CARBOXYL)PHENOXY]3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE SODIUM
SALT

5

Step 1

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(1,2-dihydro-1-isobenzofuranone-6-
oxy)3-pyridyl]ethyl}pyridine-N-oxide

To a solution of intermediate 3 (104 mg, 0.214 mmol) in 0.2 mL of pyridine,
was added 45 mg of (0.3 mmol) of phenol followed by 45 mg of K₂CO₃ and 3 mg of
CuO. The mixture was stirred at 170 °C for 3 h cooled down to room temperature and
purified directly by flash chromatography on silica gel (10% EtOH/ethyl acetate) to
afford 47 mg of the title compound.

15 Step 2

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[(4-hydroxymethyl-3-
carboxyl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide sodium salt

To a solution of lactone (23 mg, 0.041 mmol) from Step 1 above in 1
mL of ethanol, was added 0.041 mL of a 1 N solution of NaOH. The reaction was
stirred 3 h at room temperature and 1 mL of water was added. The mixture was
filtered and frozen dry to afford 22 mg of the title compound.

EXAMPLE 14

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(BENZYLOXY)3-
PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

25

Following the procedure described in Example 1 but substituting
benzyl alcohol for 4-trifluoromethoxyphenol, the title compound was obtained as a
white foam (290 mg).

¹H NMR (500 MHz, Acetone-d₆) δ 8.11 (d, 1H), 7.95 (m, 2H), 7.73
(dd, 1H), 7.45-7.25 (m, 8H), 7.18 (m, 2H), 6.96 (t, 1H), 6.93 (t, 1H), 6.77 (d, 1H),
5.33 (s, 2H), 4.49 (t, 1H), 3.45 (m, 2H).

30

EXAMPLE 15

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(1-PHENYLETHOXY)3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

Following the procedure described in Example 1 but substituting (\pm)-1-phenylethanol for 4-trifluoromethoxyphenol, the title compound was obtained as a white foam (54 mg).

^1H NMR (500 MHz, Acetone- d_6) δ 8.01 (m, 1H), 7.92 (m, 2H), 7.70 (m, 1H), 7.42-7.37 (m, 3H), 7.32-7.28 (m, 3H), 7.25-7.20 (m, 2H), 7.15 (m, 2H), 6.93 (m, 2H), 6.75 (d, 1H), 6.17 (m, 1H), 4.44 (m, 1H), 3.42 (m, 2H), 1.54 (d, 3H).

EXAMPLE 16

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(3,4-DIFLUOROBENZYLOXY)3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

Following the procedure described in Example 1 but substituting 3,4-difluorobenzyl alcohol for 4-trifluoromethoxyphenol, the title compound was obtained as an oil (370 mg).

^1H NMR (500 MHz, Acetone- d_6) δ 8.12 (d, 1H), 7.96 (m, 2H), 7.77 (dd, 1H), 7.41 (m, 2H), 7.34-7.26 (m, 4H), 7.19 (m, 2H), 6.97 (t, 1H), 6.94 (t, 1H), 6.79 (d, 1H), 5.30 (m, 2H), 4.51 (t, 1H), 3.48 (m, 2H).

EXAMPLE 17

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(4-METHYLSULFONYLBENZYLOXY)3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

Step 1

2-[4-(methylthio)benzyloxy]-5-bromopyridine

To a solution of 2,5-dibromopyridine (5.0 g, 21.1 mmol) in 75.0 mL of toluene, was added 4.2 g (27.43 mmol) of 4-(methylthio)benzyl alcohol, 2.8 g (50.64 mmol) of KOH and 400 mg (0.054 mmol) of 18-crown-6. The solution was heated at refluxing temperature with a Dean-Stark apparatus for 3 h, cooled down to room temperature and rotovaped down to dryness. The residue was diluted with water/ CHCl_3 and the organic phase was washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The solid residue was washed with Et_2O /hexane and filtered to afford 3.6 g (55%) of bromide as a pale yellow solid.

Step 2

[3,4-Bis(difluoromethoxy)phenyl]-{6-[4-(methylthio)benzyloxy]-3-pyridyl}methanol

- 5 To a -78 °C solution of bromopyridine from Step 1 above (1.0 g, 3.22 mmol) in 10 mL of THF, was added 1.7 mL (3.65 mmol) of a 2.1 M solution of *n*-BuLi. The solution was stirred 15 minutes followed by the addition of 7 mL of a THF solution of 3,4-bis(difluoromethoxy)benzaldehyde (512 mg, 2.15 mmol). The resulting solution was stirred 30 minutes at -78 °C, quenched with a 25% NH₄OAc solution and diluted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was
- 10 purified by flash chromatography on silica gel (25% Ethyl acetate/hexane) to afford the alcohol as an oil (380 mg, 30%).

15 Step 3

[3,4-Bis(difluoromethoxy)phenyl]-[6-(4-methylsulfonylbenzyloxy)3-pyridyl]methanol

- To a solution of methyl sulfide from Step 2 above (380 mg, 0.97 mmol) in a mixture of 10 mL of CH₂Cl₂ and 1.0 mL of MeOH, was added MMPP (1.4 g, 2.82 mmol) in one portion. The mixture was stirred 1.5 h at room temperature, quenched with a 25% NH₄OAc solution and diluted with ethyl acetate. The organic
- 20 layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (60% Ethyl acetate/hexane) to afford the methyl sulfone as an oil (384 mg, 93%).

25 Step 4

[3,4-Bis(difluoromethoxy)phenyl]-[6-(4-methylsulfonylbenzyloxy)3-pyridyl]chloromethane

- The procedure for the formation of the chloride described in Example 1, Step 3 was applied using the product of Step 3 above as starting material. The
- 30 chloride obtained was used directly for the next step without any purification.

Step 5

4-{1-Carbethoxy-2-[3,4-bis(difluoromethoxy)phenyl]-2-[6-(4-methylsulfonylbenzyloxy)-3-pyridyl]ethyl}pyridine

The procedure for the alkylation with ethyl 4-pyridylacetate described in Example 1, Step 4 was applied using the product of Step 4 above as starting material. The ethyl ester obtained was used directly for the next step without any purification.

5 Step 6

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-methylsulfonylbenzyloxy)3-pyridyl]ethyl}pyridine

The procedure for the hydrolysis/decarboxylation described in Example 1, Step 5 was applied using the product of Step 5 above as starting material. The
10 pyridine was obtained as an oil (340 mg, 65% for 3 steps).

Step 7

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-methylsulfonylbenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide

15 The procedure for the oxidation of the pyridine group described in Example 1, Step 6 was applied using the product of Step 6 above as starting material. The title compound was obtained as a foam (320 mg, 92%).

¹H NMR (500 MHz, Acetone-d₆) δ 8.10 (d, 1H), 7.96-7.92 (m, 4H), 7.77 (dd, 1H), 7.68 (d, 2H), 7.41 (d, 1H), 7.33 (dd, 1H), 7.27 (d, 1H), 7.18 (d, 2H),
20 6.97 (t, 1H), 6.94 (t, 1H), 6.84 (d, 1H), 5.46 (s, 2H), 4.50 (t, 1H), 3.46 (m, 2H), 3.12 (s, 3H).

EXAMPLE 18

(ENANTIOMER-1)-4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(3,5-DIFLUOROBENZYLOXY)3-PYRIDYL]ETHYL}PYRIDINE
25

Following the procedure described in Example 1, Step 1-5 but substituting 3,5-difluorobenzyl alcohol for 4-trifluoromethoxyphenol, the racemic title compound was obtained as a white foam. The mixture was then resolved with a preparative column: chiralpak AD, 17% *i*-PrOH/hexane, 70 mL/min. 650 mg of
30 Example 18 were obtained as the fast eluting enantiomer with a retention time of 38 minutes.

¹H NMR (400 MHz, Acetone-d₆) δ 8.36 (dd, 2H), 8.10 (d, 1H), 7.78 (dd, 1H), 7.40 (s, 1H), 7.32 (dd, 1H), 7.25 (d, 1H), 7.18 (dd, 2H), 7.07 (m, 2H), 6.96

(t, 1H), 6.95 (m, 1H), 6.92 (t, 1H), 6.79 (d, 1H), 5.35 (s, 2H), 4.55 (t, 1H), 3.48 (dd, 2H).

EXAMPLE 19

5 (ENANTIOMER-2)-4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(3,5-DIFLUOROBENZYLOXY)3-PYRIDYL]ETHYL}PYRIDINE

Following the procedure described in Example 1, Step 1-5 but substituting 3,5-difluorobenzyl alcohol for 4-trifluoromethoxyphenol, the racemic title compound was obtained as a white foam. The mixture was then resolved with a preparative column: chiralpak AD, 35% *i*-PrOH/hexane, 75 mL/min. 640 mg of Example 19 were obtained as the slow eluting enantiomer with a retention time of 45 minutes.

¹H NMR (400 MHz, Acetone-d₆) δ 8.36 (dd, 2H), 8.10 (d, 1H), 7.78 (dd, 1H), 7.40 (s, 1H), 7.32 (dd, 1H), 7.25 (d, 1H), 7.18 (dd, 2H), 7.07 (m, 2H), 6.96 (t, 1H), 6.95 (m, 1H), 6.92 (t, 1H), 6.79 (d, 1H), 5.35 (s, 2H), 4.55 (t, 1H), 3.48 (dd, 2H).

EXAMPLE 20

20 (ENANTIOMER-1)-4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(3,5-DIFLUOROBENZYLOXY)3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

The procedure for the oxidation of the pyridine group described in Example 1, Step 6 was applied using the product of Example 18 above as starting material. The title compound was obtained as a foam (600 mg).

¹H NMR (400 MHz, Acetone-d₆) δ 8.13 (d, 1H), 7.97 (d, 2H), 7.78 (dd, 1H), 7.41 (d, 1H), 7.34 (dd, 1H), 7.27 (d, 1H), 7.20 (d, 2H), 7.09 (dd, 2H), 6.98 (t, 1H), 6.95 (t, 1H), 6.94 (m, 1H), 6.85 (d, 1H), 5.36 (s, 2H), 4.53 (t, 1H), 3.47 (dd, 2H).

EXAMPLE 21

30 (ENANTIOMER-2)-4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(3,5-DIFLUOROBENZYLOXY)3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

The procedure for the oxidation of the pyridine group described in Example 1, Step 6 was applied using the product of Example 19 above as starting material. The title compound was obtained as a foam (600 mg).

¹H NMR (400 MHz, Acetone-d₆) δ 8.13 (d, 1H), 7.97 (d, 2H), 7.78 (dd, 1H), 7.41 (d, 1H), 7.34 (dd, 1H), 7.27 (d, 1H), 7.20 (d, 2H), 7.09 (dd, 2H), 6.98 (t, 1H), 6.95 (t, 1H), 6.94 (m, 1H), 6.85 (d, 1H), 5.36 (s, 2H), 4.53 (t, 1H), 3.47 (dd, 2H).

5

EXAMPLE 22

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-{6-[2-METHYL-2-(4-FLUOROPHENYL)PROPYLOXY]3-PYRIDYL)ETHYL}PYRIDINE

Step 1

10 2-Methyl-2-(4-fluorophenyl)propanol

To a 0 °C solution of methyl 4-fluorophenylacetate (37 mmol) in 80 mL of THF was added 83 mmol of a 1.0 M solution of NaHMDS in THF. The solution was stirred 35 minutes at 0 °C and 112 mmol of MeI were added. The reaction was stirred overnight at room temperature and quenched at 0 °C with a saturated solution of NH₄Cl. The aqueous layer was extracted with Et₂O and the combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% Et₂O/hexane) to afford the ester methyl 2-methyl-2-(4-fluorophenyl) propanoate. This ester (3.1 g) was then dissolved in 60 mL of THF and treated at 0 °C with 8 mL of a LiAlH₄ solution. The reaction was stirred 30 minutes at 0 °C and quenched with a saturated solution of NH₄Cl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (40% Et₂O/hexane) to afford 2.7 g (100%) of alcohol.

Step 2

2-[2-methyl-2-(4-fluorophenyl)propyloxy]-5-bromopyridine

Following the procedure described in Example 17, Step 1 but substituting 2-methyl-2-(4-fluorophenyl)propanol From Step 1 above for 4-(methylthio)benzyl alcohol, the desired bromopyridine was obtained in 90% yield.

30

Step 3

[3,4-Bis(difluoromethoxy)phenyl]-{6-[2-methyl-2-(4-fluorophenyl)propyloxy]-3-pyridyl}methanol

- 5 The coupling procedure described in Example 17, Step 2 was applied using the product of Step 2 above as starting material. The alcohol was obtained in 45% yield.

Step 4

10 [3,4-Bis(difluoromethoxy)phenyl]-{6-[2-methyl-2-(4-fluorophenyl)propyloxy]-3-pyridyl}chloromethane

The procedure for the formation of the chloride described in Example 1, Step 3 was applied using the product of Step 3 above as starting material. The chloride obtained was used directly for the next step without any purification.

15 Step 5

4-{1-Carbethoxy-2-[3,4-bis(difluoromethoxy)phenyl]-2-{6-[2-methyl-2-(4-fluorophenyl)propyloxy]-3-pyridyl}ethyl}pyridine

- 20 The procedure for the alkylation with ethyl 4-pyridylacetate described in Example 1, Step 4 was applied using the product of Step 4 above as starting material. The ethyl ester obtained was used directly for the next step without any purification.

Step 6

25 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-{6-[2-methyl-2-(4-fluorophenyl)propyloxy]-3-pyridyl}ethyl}pyridine

The procedure for the hydrolysis/decarboxylation described in Example 1, Step 5 was applied using the product of Step 5 above as starting material. 641 mg of the title compound were obtained (58%, 3 Steps).

- 30 ¹H NMR (400 MHz, Acetone-d₆) δ 8.36 (d, 2H), 8.06 (s, 1H), 7.69 (dd, 1H), 7.49-7.46 (m, 2H), 7.38 (s, 1H), 7.29 (q, 2H), 7.17 (d, 2H), 7.04 (t, 2H), 6.94 (t, 1H), 6.92 (t, 1H), 6.64 (d, 1H), 4.52 (t, 1H), 4.26 (s, 2H), 3.45 (d, 2H), 1.39 (s, 6H).

EXAMPLE 23

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[2-METHYL-2-(4-FLUOROPHENYL)PROPYLOXY]3-PYRIDYL)ETHYL}PYRIDINE-N-OXIDE

The procedure for the oxidation of the pyridine group described in Example 3 was applied using the product of Example 22 above as starting material. The title compound was obtained as a foam (157 mg, 62%).

¹H NMR (400 MHz, Acetone-d₆) δ 8.06 (d, 1H), 7.93 (d, 2H), 7.67 (dd, 1H), 7.50-7.47 (m, 2H), 7.38 (s, 1H), 7.32 (q, 2H), 7.17 (d, 2H), 7.04 (t, 2H), 6.95 (t, 1H), 6.92 (t, 1H), 6.65 (d, 1H), 4.48 (t, 1H), 4.27 (s, 2H), 3.44 (dd, 2H), 1.40 (s, 6H).

EXAMPLE 24

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[2-(4-FLUOROPHENYL)ETHOXY]3-PYRIDYL)ETHYL}PYRIDINE

Following the procedure described in Example 22, Step 2-6 but substituting 2-(4-fluorophenyl)ethanol for 2-methyl-2-(4-fluorophenyl)propanol, 820 mg of the title compound were obtained.

¹H NMR (400 MHz, Acetone-d₆) δ 8.39 (d, 2H), 8.09 (s, 1H), 7.71 (dd, 1H), 7.39 (s, 1H), 7.35 (m, 3H), 7.25 (d, 1H), 7.20 (m, 2H), 7.05 (m, 2H), 6.85 (t, 1H), 6.83 (t, 1H), 6.66 (d, 1H), 4.55 (t, 1H), 4.42 (t, 2H), 3.42 (d, 2H), 3.02 (t, 2H).

EXAMPLE 25

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[2-(4-FLUOROPHENYL)ETHOXY]3-PYRIDYL)ETHYL}PYRIDINE-N-OXIDE

The procedure for the oxidation of the pyridine group described in Example 3 was applied using the product of Example 24 above as starting material. The title compound was obtained as a foam (137 mg, 66%).

¹H NMR (400 MHz, Acetone-d₆) δ 8.08 (s, 1H), 7.93 (d, 2H), 7.70 (dd, 1H), 7.38 (s, 1H), 7.35 (m, 3H), 7.28 (d, 1H), 7.18 (d, 2H), 7.03 (t, 2H), 6.95 (t, 1H), 6.92 (t, 1H), 6.67 (d, 1H), 4.48 (t, 1H), 4.42 (t, 2H), 3.45 (dd, 2H), 3.01 (t, 2H).

EXAMPLE 26

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(4-TRIFLUOROMETHYLBENZYLOXY)3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

5 Following the procedure described in Example 1 but substituting 4-trifluoromethylbenzyl alcohol for 4-trifluoromethoxyphenol, 427 mg of the title compound was obtained as an oil.

¹H NMR (500 MHz, Acetone-d₆) δ 8.12 (d, 1H), 7.98 (m, 2H), 7.78 (dd, 1H), 7.70 (d, 2H), 7.65 (d, 2H), 7.43 (d, 1H), 7.33 (m, 1H), 7.28 (d, 1H), 7.20 (m, 2H), 7.00 (t, 1H), 6.96 (t, 1H), 6.83 (d, 1H), 5.43 (m, 2H), 4.52 (t, 1H), 3.47 (m, 10 2H).

EXAMPLE 27

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(4-TRIFLUOROMETHOXYBENZYLOXY)3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

15

Following the procedure described in Example 1 but substituting 4-trifluoromethoxybenzyl alcohol for 4-trifluoromethoxyphenol, 480 mg of the title compound was obtained as an oil.

¹H NMR (500 MHz, Acetone-d₆) δ 8.12 (d, 1H), 7.96 (m, 2H), 7.76 (dd, 1H), 7.57 (d, 2H), 7.41 (s, 1H), 7.32 (m, 3H), 7.27 (d, 1H), 7.19 (d, 2H), 6.98 (t, 20 1H), 6.94 (t, 1H), 6.79 (d, 1H), 5.36 (m, 2H), 4.51 (t, 1H), 3.46 (m, 2H).

EXAMPLE 28

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(1,1-DIMETHYL-2-PHENYLETHOXY)3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

25

Step 1-5

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(1,1-dimethyl-2-phenylethoxy)3-pyridyl]ethyl}pyridine

30

Following the procedure described in Example 22, Step 2-6 but substituting 1,1-dimethyl-2-phenylethanol for 2-methyl-2-(4-fluorophenyl)propanol the pyridine was obtained.

Step 6

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(1,1-dimethyl-2-phenylethoxy)3-pyridyl]ethyl}pyridine-N-oxide

- 5 The procedure for the oxidation of the pyridine group described in Example 3 was applied using the product of Step 5 above as starting material. The title compound was obtained as a foam (175 mg).

¹H NMR (400 MHz, Acetone-d₆) δ 8.12 (d, 1H), 7.95 (d, 2H), 7.67 (dd, 1H), 7.40 (d, 1H), 7.33 (dd, 1H), 7.26 (d, 1H), 7.12-7.23 (m, 7H), 6.96 (t, 1H), 6.92 (t, 1H), 6.60 (d, 1H), 4.47 (t, 1H), 3.46 (dd, 2H), 3.23 (d, 2H), 1.49 (s, 6H).

10

EXAMPLE 29

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[2-THIENYLMETHOXY]3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

15 Step 1-5

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-thienylmethoxy]3-pyridyl]ethyl}pyridine

- 20 Following the procedure described in Example 22, Step 2-6 but substituting (2-thienyl)methanol for 2-methyl-2-(4-fluorophenyl)propanol, the pyridine was obtained.

Step 6

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-thienylmethoxy]3-pyridyl]ethyl}pyridine-N-oxide

- 25 The procedure for the oxidation of the pyridine group described in Example 3 was applied using the product of Step 5 above as starting material. The title compound was obtained as a foam (35 mg).

30 ¹H NMR (400 MHz, Acetone-d₆) δ 8.14 (d, 1H), 7.95 (d, 2H), 7.73 (dd, 1H), 7.43-7.41 (m, 2H), 7.31 (q, 2H), 7.20-7.15 (m, 3H), 7.00-6.97 (m, 1H), 6.97 (t, 1H), 6.94 (t, 1H), 6.72 (d, 1H), 5.50 (s, 2H), 4.51 (t, 1H), 3.52-3.42 (m, 2H).

EXAMPLE 30

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[1-METHYL-1-(4-
FLUOROPHENYL)ETHOXY]3-PYRIDYL}ETHYL}PYRIDINE

5 Following the procedure described in Example 22, Step 2-6 but
substituting 1-methyl-1-(4-fluorophenyl)ethanol (Prepared by the addition of MeMgCl
on 4-fluoroacetophenone) for 2-methyl-2-(4-fluorophenyl)propanol, 500 mg of the
title compound were obtained.

¹H NMR (400 MHz, Acetone-d₆) δ 8.33 (d, 2H), 7.80 (d, 1H), 7.65
(dd, 1H), 7.43-7.38 (m, 2H), 7.33 (s, 1H), 7.26 (dd, 1H), 7.22 (d, 1H), 7.10 (d, 2H),
10 7.00 (t, 1H), 6.92 (t, 1H), 6.91 (t, 1H), 6.72 (d, 1H), 4.39 (t, 1H), 3.40 (m, 2H), 1.81
(s, 6H).

EXAMPLE 31

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[1-METHYL-1-(4-
15 FLUOROPHENYL)ETHOXY]3-PYRIDYL}ETHYL}PYRIDINE-N-OXIDE

The procedure for the oxidation of the pyridine group described in
Example 3 was applied using the product of Example 30 above as starting material.
The title compound was obtained as a foam (53 mg, 19%).

¹H NMR (400 MHz, Acetone-d₆) δ 7.92 (d, 2H), 7.84 (d, 1H), 7.44-
20 7.38 (m, 2H), 7.33 (s, 1H), 7.29 (dd, 1H), 7.22 (d, 1H), 7.12 (d, 2H), 7.05 (t, 2H),
6.95 (t, 1H), 6.93 (t, 1H), 6.74 (d, 1H), 4.32 (t, 1H), 3.45-3.32 (m, 2H), 1.82 (s, 6H).

EXAMPLE 32

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(4-
25 FLUOROBENZYLOXY)3-PYRIDYL}ETHYL}PYRIDINE-N-OXIDE

Following the procedure described in Example 1 but substituting 4-
fluorobenzyl alcohol for 4-trifluoromethoxyphenol, 475 mg of the title compound
were obtained.

¹H NMR (400 MHz, Acetone-d₆) δ 8.11 (d, 1H), 7.94 (d, 2H), 7.74
30 (dd, 1H), 7.47 (dd, 2H), 7.40 (d, 1H), 7.33 (dd, 1H), 7.27 (d, 1H), 7.18 (d, 2H), 7.08-
7.13 (m, 2H), 6.96 (t, 1H), 6.93 (t, 1H), 6.77 (d, 1H), 5.30 (s, 2H), 4.50 (t, 1H), 3.47
(dd, 2H).

EXAMPLE 33

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-(4-CHLOROBENZYLOXY)3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

5 Following the procedure described in Example 1 but substituting 4-chlorobenzyl alcohol for 4-trifluoromethoxyphenol, 500 mg of the title compound were obtained.

^1H NMR (400 MHz, Acetone- d_6) δ 8.11 (d, 1H), 7.94 (d, 2H), 7.75 (dd, 1H), 7.46 (d, 2H), 7.36-7.41 (m, 3H), 7.33 (dd, 1H), 7.27 (d, 1H), 7.18 (d, 2H), 6.97 (t, 1H), 6.93 (t, 1H), 6.77 (d, 1H), 5.31 (s, 2H), 4.49 (t, 1H), 3.46 (dd, 2H).

10

EXAMPLE 34

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-[6-[1,2-DIHYDRO-1-ISOBENZOFURANONE-6-OXY]3-PYRIDYL]ETHYL}PYRIDINE-N-OXIDE

15 To a solution of intermediate 3 (104 mg, 0.214 mmol) in 0.2 mL of pyridine, was added 45 mg of (0.3 mmol) of 6-hydroxyl-1,2-dihydro-1-isobenzofuranone followed by 45 mg of K_2CO_3 and 3 mg of CuO. The mixture was stirred at 170 °C for 3 h cooled down to room temperature and purified directly by flash chromatography on silica gel (10% EtOH/ethyl acetate) to afford 47 mg of the title compound.

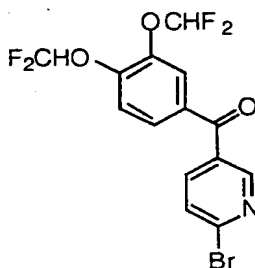
20

^1H NMR (500 MHz, Acetone- d_6) δ 8.11 (s, 1H), 8.00-7.90 (m, 3 H), 7.69 (d, 1H), 7.55-7.47 (m, 2H), 7.44 (s, 1H), 7.34 (d, 1H), 7.28 (d, 1H), 7.20 (d, 2H), 7.03 (d, 1H), 6.97 (t, large J, 1H), 6.94 (t, large J, 1H), 5.40 (s, 2H), 4.57 (t, 1H), 3.50 (d, 2H).

PREPARATION OF INTERMEDIATES

INTERMEDIATE 1

[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-(6-BROMO-3-PYRIDYL)METHANONE



1

Step 1

[3,4-Bis(difluoromethoxy)phenyl]-(6-bromo-3-pyridyl)methanol

To a -78 °C suspension of 2,5-dibromopyridine (11.4 g, 48.0 mmol) in 300 mL of Et₂O, was added 40.0 mL (48.0 mmol) of a 1.2 N solution of *n*-butyllithium in hexane over 10 minutes. The orange mixture was stirred (Mechanical stirrer) 10 minutes at -78 °C followed by the addition over 5 minutes of a precooled solution of bis(difluoromethoxy)benzaldehyde (9.6 g, 40.0 mmol) in 60 mL of Et₂O. This red solution was stirred 1 h at -78 °C and slowly poured into a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted with ethyl acetate and the combined organic phases were washed with brine, dry over MgSO₄ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (Gradient 20% to 40% ethyl acetate/hexane) to afford 8.3 g (53%) of alcohol.

Step 2

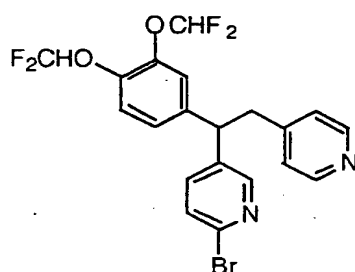
[3,4-Bis(difluoromethoxy)phenyl]-(6-bromo-3-pyridyl)methanone

To a solution of alcohol (3.96 g, 10.0 mmol) from Step 1 above in 60 mL of CH₂Cl₂, was added 8.1 g (93.0 mmol) of MnO₂. The resulting mixture was stirred 20 h at room temperature and filtered on celite. the volatile were removed under reduced pressure to afford 3.48 g (88%) of ketone.

¹H NMR (500 MHz, Acetone-d₆) δ 8.72 (d, 1H), 8.10 (dd, 1H), 7.85-7.78 (m, 3H), 7.55 (d, 1H), 7.20 (t, 1H), 7.12 (t, 1H).

INTERMEDIATE 2

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-(6-BROMO-3-PYRIDYL)ETHYL}PYRIDINE



5

2

Step 1

[3,4-Bis(difluoromethoxy)phenyl]-(6-bromo-3-pyridyl)chloromethane

To a solution [3,4-Bis(difluoromethoxy)phenyl]-(6-bromo-3-pyridyl)methanol (15.8 g, 40.0 mmol) in 400 mL of CH₂Cl₂, was added 3.8 mL (52.0 mmol) of SOCl₂. The solution was stirred 45 minutes at room temperature and poured into a saturated aqueous solution of NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dry over MgSO₄ and concentrated under reduced pressure. The crude chloride was used directly for the next step without any purification.

15

Step 2

4-{1-Carbethoxy-2-[3,4-bis(difluoromethoxy)phenyl]-2-(6-bromo-3-pyridyl)ethyl}pyridine

To a 0 °C solution of ethyl 4-pyridyl acetate (19.8 g, 120 mmol) in 500 mL of THF, was added 21.0 mL (120 mmol) of HMPA and 240 mL (120 mmol) of a 0.5 M solution KHMDS in toluene. The resulting mixture was stirred 15 minutes at room temperature followed by the addition over 10 minutes of a solution of the crude chloride from Step 1 above in 100 mL of THF. The reaction was stirred 1 h at room temperature, poured into a saturated aqueous solution of NH₄Cl and the pH was adjusted to 7 with 1 N HCl. The aqueous layer was extracted with ethyl acetate and the combined organic phases were washed with brine, dry over MgSO₄ and

25

concentrated under reduced pressure. The residue was used directly for the next step without any purification.

Step 3

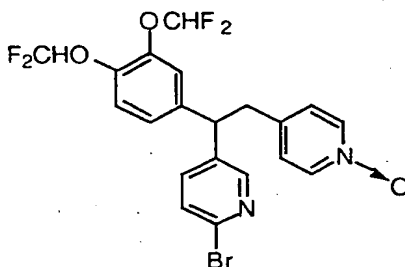
5 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-(6-bromo-3-pyridyl)ethyl}pyridine

To a solution of crude ester from Step 2 above in a mixture of 540 mL of THF, 180 mL of MeOH and 180 mL of water, was added 180 mL of a 2 N solution of LiOH. The solution was stirred 1.5 h at 65 °C, cooled down to room temperature and 360 mL of 1 N HCl solution were added. The mixture was rotovaped down, the
10 residue was diluted in ethyl acetate and the organic phases was washed with brine, dry over MgSO₄ and concentrated under reduced pressure to afford 18.2 g (97%, 3 steps) of pure bromopyridine.

¹H NMR (500 MHz, Acetone-d₆) δ 8.40 (m, 3H), 7.78 (dd, 1H), 7.50 (d, 1H),
7.43 (s, 1H), 7.36 (dd, 1H), 7.28 (d, 1H), 7.20 (m, 2H), 6.95 (t, 1H), 6.94 (t, 1H),
15 4.65 (t, 1H), 3.58-3.48 (m, 2H).

INTERMEDIATE 3

4-{2-[3,4-BIS(DIFLUOROMETHOXY)PHENYL]-2-(6-BROMO-3-PYRIDYL)ETHYL}PYRIDINE



3

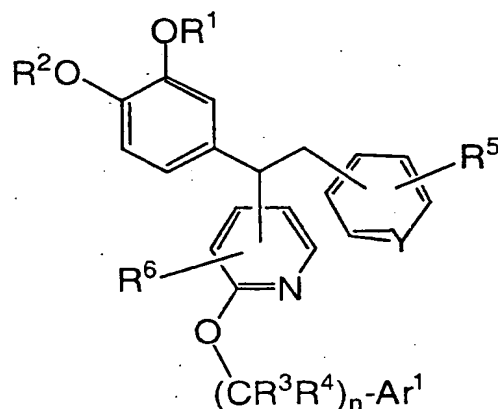
20

To a solution of intermediate 2 (2.0 g, 4.2 mmol) in a mixture of 30 mL of CH₂Cl₂ and 3 mL of MeOH was added 1.55 g (2.5 mmol) of 80% MMPP. The reaction was stirred at room temperature for 20 h and purified directly by chromatography on silica gel (Gradient 3% Et₃N/ethyl acetate to 30% EtOH/ethyl
25 acetate + 3% Et₃N to 40% EtOH/ethyl acetate + 3% Et₃N) to afford 1.91 g (93%) of desired pyridine-N-oxide.

^1H NMR (500 MHz, Acetone- d_6) δ 8.38 (d, 1H), 7.95 (d, 2H), 7.77 (dd, 1H), 7.51 (d, 1H), 7.41 (s, 1H), 7.35 (dd, 1H), 7.29 (d, 1H), 7.19 (d, 2H), 6.96 (t, 1H), 6.94 (t, 1H), 4.60 (t, 1H), 3.57-3.47 (m, 2H).

WHAT IS CLAIMED IS:

1. A compound represented by formula I:



5. or a pharmaceutically acceptable salt or hydrate thereof wherein:
Y represents N or N-oxide;

R¹ and R² are independently selected from:
H, C₁-6alkyl and haloC₁-6 alkyl,

10

R³ and R⁴ are independently selected from H and C₁-6alkyl, or R³ and R⁴ attached to the same carbon atom taken together represent a carbonyl oxygen atom, or

R³ and R⁴ attached to different carbon atoms considered in combination with the carbon atoms to which they are attached along with any

- 15 intervening atoms and represent a saturated 5, 6 or 7 membered carbocyclic ring,

R⁵ and R⁶ independently represent a member selected from the group consisting of: H, C₁-6alkyl, haloC₁-6alkyl and CN;

n represents an integer of from 0-6;

- 20 Ar¹ is selected from the group consisting of:

- (a) thienyl,
- (b) thiazolyl,
- (c) pyridyl,
- (d) phenyl and
- 25 (e) naphthyl,

said Ar¹ being optionally substituted with 1-3 members selected from the group consisting of:

- (1) halo,
- 5 (2) C₁₋₆alkoxy,
- (3) C₁₋₇alkylthio,
- (4) CN,
- (5) C₁₋₆alkyl,
- (6) C₁₋₆hydroxyalkyl,
- 10 (7) -CO₂H, -CO₂C₁₋₆alkyl,
- (8) NH(SO₂Me), N(SO₂Me)₂,
- (9) SO₂Me,
- (10) NO₂,
- (11) C₁₋₆alkenyl,
- 15 (12) halo C₁₋₆ alkyl, and
- (13) NH₂,

and when Ar¹ represents a phenyl or naphthyl group with two or three substituents, two such substituents may be considered in combination and represent a
20 5 or 6 membered fused lactone ring.

2. A compound in accordance with claim 1 wherein R¹ and R² are C₁₋₆ alkyl or haloC₁₋₆alkyl.

25 3. A compound in accordance with claim 2 wherein R¹ and R² are selected from the group consisting of CH₃, CH₂F, CHF₂ and CF₃.

4. A compound in accordance with claim 3 wherein R¹ and R² are CHF₂.
30

5. A compound in accordance with claim 1 wherein n is selected from 0, 1, 2 and 3.

35 6. A compound in accordance with claim 5 wherein n is selected from 0, 1 and 2.

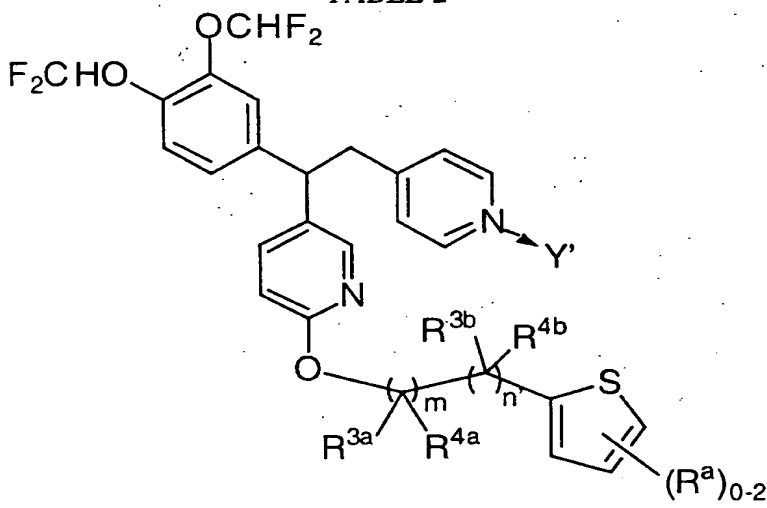
7. A compound in accordance with claim 1 wherein R⁵ and R⁶ are independently selected from the group consisting of: H and C₁₋₆ alkyl.
- 5 8. A compound in accordance with claim 7 wherein R⁵ and R⁶ represent H.
9. A compound in accordance with claim 1 wherein Ar¹ is selected from phenyl and naphthyl.
- 10 10. A compound in accordance with claim 9 wherein Ar¹ is phenyl.
11. A compound in accordance with claim 1 wherein R³ and R⁴ are H or C₁₋₆alkyl.
- 15 12. A compound in accordance with claim 11 wherein R³ and R⁴ are H or methyl.
13. A compound in accordance with claim 1 wherein:
20 R¹ and R² are C₁₋₆alkyl or haloC₁₋₆alkyl selected from the group consisting of CH₃, CH₂F, CHF₂ and CF₃ ;
n is 0, 1, 2 or 3;
Ar¹ is phenyl or naphthyl,
R³ and R⁴ are H or methyl
25 and R⁵ and R⁶ are H or C₁₋₆alkyl.
14. A compound in accordance with claim 13 wherein:
R¹ and R² are CHF₂, and n is 0, 1 or 2.
15. A compound in accordance with claim 14 wherein:
30 R¹ and R² are CHF₂;
n is 0, 1 or 2;
R³ and R⁴ are H or methyl and
Ar¹ is phenyl.

16. A compound selected from the group consisting of:
- 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(trifluoromethoxy)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 - 5 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-(methoxycarbonyl)phenoxy)3-pyridyl]ethyl}pyridine,
 - 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-(methoxycarbonyl)phenoxy)3-pyridyl]ethyl}pyridine-N-oxide,
 - 10 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(2-hydroxypropan-2-yl)phenoxy]3-pyridyl]ethyl}pyridine,
 - 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(2-hydroxypropan-2-yl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 - 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-nitrophenoxy)3-pyridyl]ethyl}pyridine-N-oxide,
 - 15 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(methylsulfonylamino)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 - 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(trifluoromethyl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 - 20 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[3-(methylsulfonylamino)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 - 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(2-propenyl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 - 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(2-propyl)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 - 25 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[4-(dimethylsulfonylamino)phenoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 - 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[(4-hydroxymethyl)-3-carboxyl]phenoxy]3-pyridyl]ethyl}pyridine-N-oxide sodium salt,
 - 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(benzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
 - 30 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(1-phenylethoxy)3-pyridyl]ethyl}pyridine-N-oxide,
 - 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,4-difluorobenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,

- 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-methylsulfonylbenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
 (Enantiomer-1)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,5-difluorobenzyloxy)3-pyridyl]ethyl}pyridine,
 5 (Enantiomer-2)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,5-difluorobenzyloxy)3-pyridyl]ethyl}pyridine,
 (Enantiomer-1)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,5-difluorobenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
 (Enantiomer-2)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(3,5-difluorobenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
 10 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-methyl-2-(4-fluorophenyl)propyloxy]3-pyridyl]ethyl}pyridine,
 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-methyl-2-(4-fluorophenyl)propyloxy]3-pyridyl]ethyl}pyridine-N-oxide,
 15 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-(4-fluorophenyl)ethoxy]3-pyridyl]ethyl}pyridine,
 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[2-(4-fluorophenyl)ethoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-trifluoromethylbenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
 20 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-trifluoromethoxybenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(1,1-dimethyl-2-phenylethoxy)3-pyridyl]ethyl}pyridine-N-oxide,
 25 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(2-thienylmethoxy)3-pyridyl]ethyl}pyridine-N-oxide,
 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[1-methyl-1-(4-fluorophenyl)ethoxy]3-pyridyl]ethyl}pyridine,
 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-[1-methyl-1-(4-fluorophenyl)ethoxy]3-pyridyl]ethyl}pyridine-N-oxide,
 30 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-fluorobenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide,
 4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[6-(4-chlorobenzyloxy)3-pyridyl]ethyl}pyridine-N-oxide, and

4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-{6-[1,2-dihydro-1-isobenzofuranone-6-oxy]3-pyridyl}ethyl}pyridine-N-oxide;
or a pharmaceutically acceptable salt or hydrate thereof.

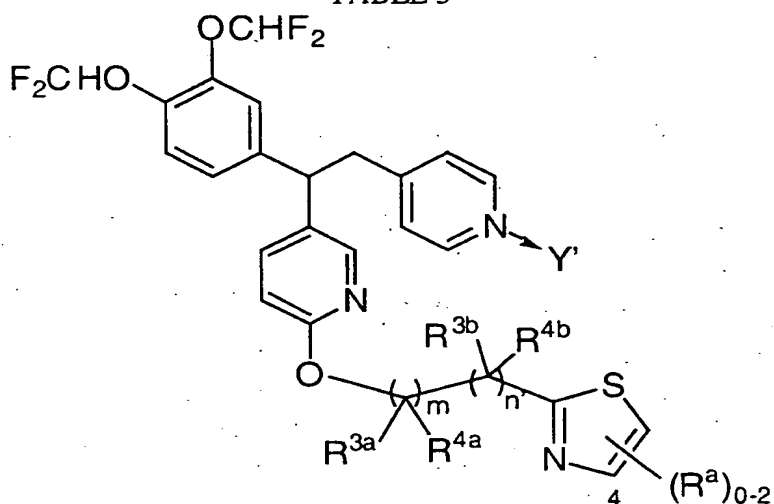
- 5 17. A compound in accordance with claim 1 selected from one of the following tables:

TABLE 2								
								
Y'	M	R ^{3a}	R ^{4a}	n'	R ^{3b}	R ^{4b}	R ^a	
O	0	-	-	0	-	-	4-(trifluoromethoxy)	
-	0	-	-	0	-	-	4-(methoxycarbonyl)	
O	0	-	-	0	-	-	4-(methoxycarbonyl)	
-	0	-	-	0	-	-	4-(2-hydroxypropan-2-yl)	
O	0	-	-	0	-	-	4-(2-hydroxypropan-2-yl)	
O	0	-	-	0	-	-	4-nitro	
O	0	-	-	0	-	-	4-(methylsulphonyl amino)	
O	0	-	-	0	-	-	4-(trifluoromethyl)	

O	0	-	-	0	-	-	5-(methylsulphonyl amino)
O	0	-	-	0	-	-	4-(2-propenyl)
O	0	-	-	0	-	-	4-(2-propyl)
O	0	-	-	0	-	-	4-(dimethylsulphonyl amino)
O	0	-	-	0	-	-	4-(hydroxymethyl)-5-(carboxyl)

O	1	H	H	0	-	-	-
O	1	Me	H	0	-	-	-
O	1	H	H	0	-	-	4,5-difluoro
O	1	H	H	0	-	-	4-(methylsulfonyl)
-	1	H	H	0	-	-	3-fluoro
-	1	H	H	0	-	-	4,5-difluoro
O	1	H	H	0	-	-	4,5-dichloro
O	1	H	H	0	-	-	5-fluoro
-	1	H	H	1	Me	Me	4-fluoro
O	1	H	H	1	Me	Me	4-fluoro
-	1	H	H	1	H	H	5-fluoro
O	1	H	H	1	H	H	4-fluoro
O	1	H	H	0	-	-	4-(trifluoromethyl)
O	1	H	H	0	-	-	4-(trifluoromethoxy)
O	1	Me	Me	1	H	H	-
O	1	H	H	0	-	-	-
-	1	Me	Me	0	-	-	4-fluoro
O	1	Me	Me	0	-	-	4-fluoro
O	1	H	H	0	-	-	4-fluoro
O	1	H	H	0	-	-	4-chloro

TABLE 3

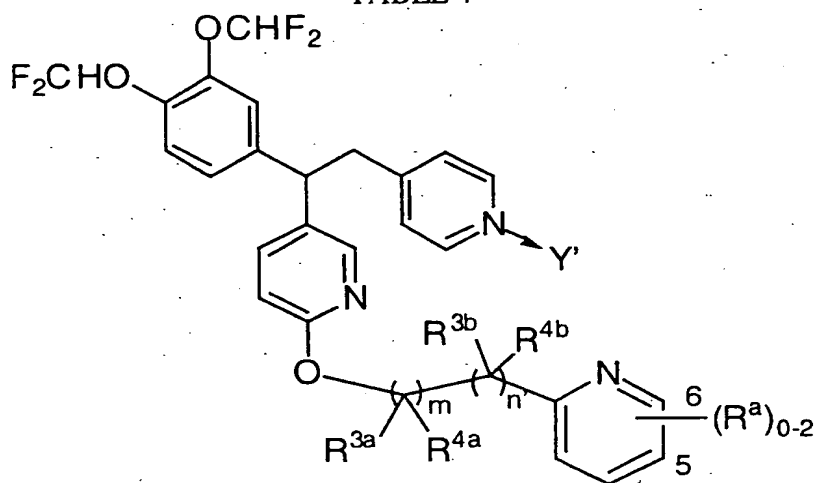


Y'	M	R ^{3a}	R ^{4a}	n'	R ^{3b}	R ^{4b}	R ^a
O	0	-	-	0	-	-	4-(trifluoromethoxy)
-	0	-	-	0	-	-	4-(methoxycarbonyl)
O	0	-	-	0	-	-	4-(methoxycarbonyl)
-	0	-	-	0	-	-	4-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	4-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	4-nitro
O	0	-	-	0	-	-	4-(methylsulphonyl amino)
O	0	-	-	0	-	-	4-(trifluoromethyl)
O	0	-	-	0	-	-	5-(methylsulphonyl amino)
O	0	-	-	0	-	-	4-(2-propenyl)
O	0	-	-	0	-	-	4-(2-propyl)
O	0	-	-	0	-	-	4-(dimethylsulphonyl amino)

O	0	-	-	0	-	-	4-(hydroxymethyl)-5-(carboxyl)
---	---	---	---	---	---	---	--------------------------------

	O	1	H	H	0	-	-	-
	O	1	Me	H	0	-	-	-
	O	1	H	H	0	-	-	4,5-difluoro
	O	1	H	H	0	-	-	4-(methylsulfonyl)
	-	1	H	H	0	-	-	4,5-dichloro
	-	1	H	H	0	-	-	5-fluoro
	O	1	H	H	0	-	-	4,5-dichloro
	O	1	H	H	0	-	-	5-fluoro
	-	1	H	H	1	Me	Me	4-fluoro
	O	1	H	H	1	Me	Me	4-fluoro
	-	1	H	H	1	H	H	4-fluoro
	O	1	H	H	1	H	H	4-fluoro
	O	1	H	H	0	-	-	4-(trifluoromethyl)
	O	1	H	H	0	-	-	4-(trifluoromethoxy)
	O	1	Me	Me	1	H	H	-
	O	1	H	H	0	-	-	-
	-	1	Me	Me	0	-	-	4-fluoro
	O	1	Me	Me	0	-	-	4-fluoro
	O	1	H	H	0	-	-	4-fluoro
	O	1	H	H	0	-	-	4-chloro

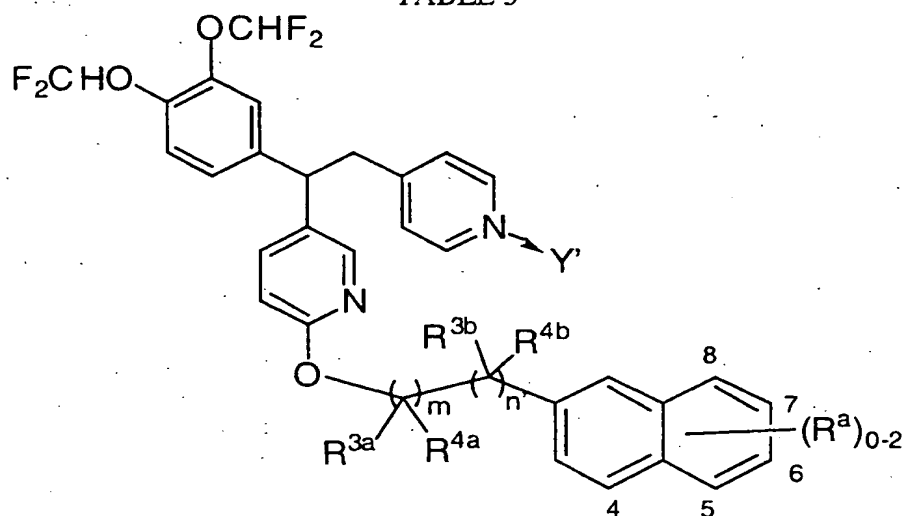
TABLE 4



Y'	M	R ^{3a}	R ^{4a}	n'	R ^{3b}	R ^{4b}	R ^a
O	0	-	-	0	-	-	6-(trifluoromethoxy)
-	0	-	-	0	-	-	6-(methoxycarbonyl)
O	0	-	-	0	-	-	6-(methoxycarbonyl)
-	0	-	-	0	-	-	6-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	6-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	6-nitro
O	0	-	-	0	-	-	6-(methylsulphonyl amino)
O	0	-	-	0	-	-	6-(trifluoromethyl)
O	0	-	-	0	-	-	5-(methylsulphonyl amino)
O	0	-	-	0	-	-	6-(2-propenyl)
O	0	-	-	0	-	-	6-(2-propyl)
O	0	-	-	0	-	-	6-(dimethylsulphonyl amino)
O	0	-	-	0	-	-	5-(hydroxymethyl)-6-(carboxyl)
O	1	H	H	0	-	-	-

O	1	Me	H	0	-	-	-
O	1	H	H	0	-	-	5,6-difluoro
O	1	H	H	0	-	-	6-(methylsulfonyl)
-	1	H	H	0	-	-	4,6-difluoro
-	1	H	H	0	-	-	5,6-dichloro
O	1	H	H	0	-	-	4,6-difluoro
O	1	H	H	0	-	-	5,6-dimethyl
-	1	H	H	1	Me	Me	6-fluoro
O	1	H	H	1	Me	Me	6-fluoro
-	1	H	H	1	H	H	6-fluoro
O	1	H	H	1	H	H	6-fluoro
O	1	H	H	0	-	-	6-(trifluoromethyl)
O	1	H	H	0	-	-	6-(trifluoromethoxy)
O	1	Me	Me	1	H	H	-
O	1	H	H	0	-	-	-
-	1	Me	Me	0	-	-	6-fluoro
O	1	Me	Me	0	-	-	6-fluoro
O	1	H	H	0	-	-	6-fluoro
O	1	H	H	0	-	-	6-fluoro

TABLE 5



Y'	M	R ^{3a}	R ^{4a}	n'	R ^{3b}	R ^{4b}	R ^a
O	0	-	-	0	-	-	7-(trifluoromethoxy)
-	0	-	-	0	-	-	7-(methoxycarbonyl)
O	0	-	-	0	-	-	7-(methoxycarbonyl)
-	0	-	-	0	-	-	7-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	7-(2-hydroxypropan-2-yl)
O	0	-	-	0	-	-	7-nitro
O	0	-	-	0	-	-	7-(methylsulphonyl amino)
O	0	-	-	0	-	-	7-(trifluoromethyl)
O	0	-	-	0	-	-	6-(methylsulphonyl amino)
O	0	-	-	0	-	-	7-(2-propenyl)
O	0	-	-	0	-	-	7-(2-propyl)
O	0	-	-	0	-	-	7-(dimethylsulphonyl amino)
O	0	-	-	0	-	-	6-(hydroxymethyl)-7-(carboxyl)

O	1	H	H	0	-	-	-
O	1	Me	H	0	-	-	-
O	1	H	H	0	-	-	6,7-difluoro
O	1	H	H	0	-	-	7-(methylsulfonyl)
-	1	H	H	0	-	-	6,7-difluoro
-	1	H	H	0	-	-	5,7-difluoro
O	1	H	H	0	-	-	5-fluoro
O	1	H	H	0	-	-	6-fluoro
-	1	H	H	1	Me	Me	7-fluoro
O	1	H	H	1	Me	Me	7-fluoro
-	1	H	H	1	H	H	7-fluoro
O	1	H	H	1	H	H	7-fluoro
O	1	H	H	0	-	-	7-(trifluoromethyl)
O	1	H	H	0	-	-	7-(trifluoromethoxy)
O	1	Me	Me	1	H	H	-
O	1	H	H	0	-	-	-
-	1	Me	Me	0	-	-	7-fluoro
O	1	Me	Me	0	-	-	7-fluoro
O	1	H	H	0	-	-	7-fluoro
O	1	H	H	0	-	-	7-chloro

18. A pharmaceutical composition that is comprised of a compound of formula (I) or a pharmaceutically acceptable salt or hydrate thereof, as defined in any one of claims 1 to 17 in combination with a pharmaceutically acceptable carrier.

19. A method of treating or preventing a disease or condition mediated by PDE 4, comprising administering to a mammalian patient in need thereof, a compound in accordance with claim 1 in an amount that is effective to treat or prevent said disease or condition.

20. A method in accordance with claim 19 wherein the disease or condition is selected from the group consisting of:

asthma, inflamed lung associated with asthma, cystic fibrosis, inflammatory airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis, other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium or brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth and cancerous invasion of normal tissues.

21. A method of treating or preventing asthma in a mammalian patient in need of such treatment or prevention, comprising administering to said patient a compound in accordance with claim 1 in an amount that is effective for treating or preventing asthma.

22. A compound of formula (I), or a pharmaceutically acceptable salt or hydrate thereof, as defined in any one of claims 1 to 17 for use in treating or preventing a disease or condition mediated by PDE 4.

23. Use of a compound of formula (I), or a pharmaceutically acceptable salt or hydrate thereof, as defined in any one of claims 1 to 17, for use in the manufacture of a medicament for treating or preventing a disease or condition mediated by PDE 4.

24. A phosphodiesterase IV (PDE 4) inhibitor pharmaceutical composition comprising an acceptable PDE 4 inhibiting amount of a compound of formula (I), as defined in any one of claims 1 to 17, or a pharmaceutically acceptable salt or hydrate thereof, in association with a pharmaceutically acceptable carrier.